THE JOURNAL OF
PEDIATRICS

JUNE 1961 *Volume* 58 *Number* 6

Delayed maturation in development

R. S. Illingworth, M.D. (Leeds), F.R.C.P., D.P.H., D.C.H.*

SHEFFIELD, ENGLAND

THERE are variations in physical growth, in teething, in the closure of the fontanel, in the separation of the prepuce, in the age of puberty, and in other aspects of physical development. Macdonald and Emery[9] have studied the differences in the rate of histologic maturation of organs. There are wide variations in intelligence and in the rate of development in various fields in children of the same level of intelligence. Some children, though they later reached a high intellectual level, were late in learning to walk, talk, acquire clean habits, read, or spell, or were uniformly retarded in the early weeks. These differences are commonly ascribed to differences in the rate of maturation of the nervous system and, probably, in myelination, which in turn may depend on enzyme systems. Dekaban[2] in his book on pediatric neurology attempted to relate the various milestones of development to the histologic changes in the nervous system.

Because I feel that insufficient attention has been paid to delayed maturation in developmental assessment, I have attempted to collect together examples of this delay in many different fields of development. The examples described are all children seen by me at the Children's Hospital, and the Jessop Maternity Hospital, Sheffield.

GENERAL DELAY IN MATURATION

Newborn infants delivered normally at term after a normal pregnancy vary greatly in their appearance of maturity. Some, for

From the University of Sheffield, Sheffield, England.

**Address, Children's Hospital, Western Bank, Sheffield 10, England.*

instance, sleep for the larger part of the day and night, make few demands for food, regurgitate readily, and suck badly, while others are wide awake and alert, sleep little during the day, are eager for food, suck well, and are correspondingly advanced in motor development.

When an infant in the first few weeks of life shows delayed progress in all aspects of development, by far the commonest cause is mental subnormality. It is important to remember, however, that quite considerable retardation can occur in all fields of development in the first few weeks of the life of a child who will prove to have a normal or superior level of intelligence in later years. Sometimes this appears to be at least partly due to poor environmental circumstances, such as emotional deprivation. The following is an example.

Case 1. This baby was seen by me for assessment for adoption when he was 6½ months old (28 weeks). He was an illegitimate child whose mother and mother's mother were mentally defective. There was little developmental history. He would not hold a rattle placed in the hand until he was 24 weeks old.

On examination he made no effort to get hold of a rattle, though he showed interest in it. He bore no weight on the legs and his head control (when pulled to the sitting position and in the prone) was that of an 18-week-old baby. I wrote, "There is no doubt that J. is fairly considerably retarded, being about the 18 week level in all fields. This may be the result of being in an institution since the age of a fortnight, and it is perfectly possible that in a good foster home he would catch up to the normal."

He was immediately placed in a foster home, and I saw him a year later, when he was 18 months old. I was disappointed with his progress. He was unable to say any words, and he could not get a spoon to the mouth. He was not nearly able to walk. He had begun to sit unsupported and to grasp objects voluntarily at 13 months and to stand holding on to furniture and to creep at 15 months. He had begun to hold his arms out for clothes at 17 months. On examination he was in no way more advanced than a 12-month-old baby. The grasp was immature. He was matching cubes and he would hand a cube on request.

Maturation accelerated subsequently, and at 5 years of age his I.Q. score was 114. He was doing well at school and had no mechanical disability.

This boy was unusual, in that he did not make the rapid strides forward which one expects when a child whose retardation is of environmental origin is placed in a good foster home. His acceleration in development occurred after the age of 18 months.

In other children there was evidence of severe birth trauma.

Case 2. This is an example of delayed maturation following a proved cerebral hemorrhage. This girl was born at term, after a normal pregnancy and delivery, weighing 8 pounds, 2 ounces. She cried normally and her color was good. When she was 36 hours old, she became pale and cyanosed, and her eyes were staring. She had a series of major convulsions, her temperature rose to 100° F., the fontanel bulged, and she became gravely ill. A subdural tap was negative, but a lumbar puncture showed a uniformly blood-stained fluid, with xanthochromic supernatant fluid. Further major convulsions occurred for 4 days. Repeated lumbar punctures were performed on account of persistent vomiting with a bulging fontanel, and on each occasion the cerebral spinal fluid was uniformly blood stained. She became severely dehydrated as a result of the vomiting, and an intravenous drip was given. The last lumbar puncture was performed at 6 weeks of age, when the fluid was merely xanthochromic.

She was gravely ill for 4 weeks, but was much better at 6 weeks. She began to smile at 7 weeks, but at 9 weeks there was no head control at all in any position (prone, ventral suspension, or when pulled to the sitting position). At 16 weeks her head control was that of a 6-week-old baby; at 24 weeks it was that of a 3-month-old baby. At 28 weeks she began to grasp objects

voluntarily. She sat without support at 8 months, pulled herself to the standing position at 10 months, walked alone at 18 months, and joined words together at 21 months. At 26 months her development was in all ways up to the average. At 5 years of age her I.Q. score was 100. There was no mechanical disability. At 6 years she had a major convulsion, but no more fits occurred in the next 2 years, while under antiepileptic treatment.

Case 3. This child caused grave anxiety about his future mental state. He was born normally at term, but had a series of major convulsions for the next 3 weeks. Subdural taps were negative. An air encephalogram was thought to show cortical atrophy. He began to smile at 2 months, but he had complete head lag in ventral suspension and when pulled to the sitting position. At 4½ months his head control was that of a child of 2½ months. By the age of 10 months, it was clear that he was average in development. At the age of 9 years he was a bright normal child with an I.Q. score of 122.

Case 4. Another child with a slow start achieved the same score. She weighed 4 pounds, 13 ounces at birth, and was well in the newborn period. At 13 weeks she had complete head lag in ventral suspension and when pulled to the sitting position. She took no notice of her surroundings until 17 weeks of age, when she "woke up," to use her mother's words. She began to smile at 18 weeks. At 21 weeks her head control was better, and at 25 weeks it corresponded to that of an average 16-week-old child. She was able to sit for a few seconds at 7½ months. At 12 months she was able to walk with one hand held and to say 10 words with meaning. Her I.Q. score at the age of 6 years was 122.

Case 5. This girl showed retarded maturation in all fields, especially, however, in motor development. She was born 6 weeks prematurely, weighing 4 pounds, 5 ounces. She began to smile at 4 months, and she was very retarded in motor development. At 1 year she was not nearly able to sit, and her head control was that of a child of 4½ months. When she was 17 months old, the diagnosis of mental retardation was made in another hospital. At 22 months she was able to stand holding on to furniture. She first learnt to walk at 50 months. At 8 years her I.Q. score was 118, and there was no mechanical disability.

Case 6. Although this infant had severe retardation in the early weeks, she later proved to have a mild degree of cerebral palsy of the ataxic type, with an I.Q. test score of 110. She had been born normal at term, though the mother had had toxemia during the pregnancy. The child took no notice of her surroundings until she was 6 months old, when she began to smile. She began to grasp objects at 9 months, to say single words at 23 months, and to join words together at 38 months. At 33 months she was slobbering, casting objects to the floor like a child of 12 months, and able to build a tower of 2 cubes. At the age of 7 years her I.Q. score was 110, and she had slight ataxia.

When unexpected improvement occurs in severely retarded infants, it is much more common to find in later years that there is some degree of residual subnormality. Examples can be summarized as follows:

Case 7. This full-term infant had convulsions on the second day. He smiled at 3½ months. The general level of development at 9 months (e.g., head control, holding object placed in hand for seconds) was that of a 3-month-old baby. Sitting occurred at 2 years of age, walking at 3 years. At 10 years of age he was at the bottom of the class in normal school, with an I.Q. of 88.

Case 8. This full-term child appeared normal in the newborn period. He took no notice of the surroundings until 9 months of age, when smiling began. He grasped objects voluntarily at 9 months and sat unsupported at 13 months. Major convulsions began at this age. The general level at 18 months was that of an 8-month-old baby. I.Q. score at 5 years was 77 with no mechanical disability.

Case 9. A full-term infant, well in the neonatal period, took no notice of the surroundings until 4 months of age. He crept at

19 months; walked at 24 months; said 5 words at 35 months, and was able to creep upstairs, but unable to get downstairs by this time. At 7 years of age he had an I.Q. of 92. Cerebral palsy was not present.

Case 10. This full-term baby smiled at 6 months, grasped at 9 months, fed himself and walked unsupported at 29 months, and spoke sentences at 3 years. His I.Q. was 90. Mild ataxia was present.

Case 11. This full-term infant took no notice of the surroundings in the first year, he just lay still, without kicking the legs or responding to overtures. At 12 months he began to smile; had major convulsions at 26 months; and said single words at 30 months. At 7 years he was an interested, alert child with occasional convulsions, mild spastic quadriplegia, and an I.Q. of 81.

Case 12. This premature baby weighed 2.0 pounds at birth. The mother had toxemia. For the first 8 months he just lay in his carriage, taking no notice of the surroundings. He smiled at 8 months. When he was 5 years old, the I.Q. score was 75. He had athetosis.

Case 13. This full-term child smiled at 3 months, sat unsupported by 12 months, walked by 24 months, managed a cup by 29 months, and had clean habits by day. He said odd words by 33 months. His I.Q. at 6.0 years was 87.

Case 14. This child was born at full term, by a difficult forceps delivery. He had grade 2 anoxia. On the fifth day he was lethargic and hypotonic. The Moro reflex was absent and the subdural tap was negative. At 8 weeks he had no head control. At 17 weeks there was persistent asymmetrical tonic neck and grasp reflex, but head control was beginning. By 8 months he was sitting. The diagnosis was minimal birth injury, with good prognosis. By 10 months he was normal in all respects. At 5 years old his I.Q. was 87, with no disability.

Case 15. I was able to follow this baby from birth. She was born 4 weeks prematurely weighing 4 pounds, 10 ounces. She was edematous for 2 days. On the fourth day she became very lethargic, lost the Moro reflex, and became difficult to feed. She remained ill for 14 days. At 15 weeks (corrected age 11 weeks) she showed motor retardation and her head control was that of a 6-week-old baby. She had begun to smile at the corrected age of 8 weeks. At 7 months her motor development was that of a 3-month-old baby. She began to chew at 9 months, to sit for a few seconds at 10½ months, and to imitate at 1 year. When she was 10½ months old, I wrote in the notes that I guessed that she would learn to walk at 21 to 24 months. At 17 months she was able to say 3 words. She walked unaided at 22 months. At 37 months she joined words together. At the age of 8 years her I.Q. score was 90.

Need for caution in diagnosis of mental subnormality. These examples indicate the need for caution in the diagnosis of mental subnormality in infancy. Delayed maturation of this degree is definitely unusual, and the great majority of infants showing the degree of retardation present in the cases described will prove to be severely subnormal in later years. The fact that so much unexpected improvement can occur, however, should always make one cautious about giving a gloomy prognosis in the early weeks. Serial head circumference measurements are valuable in the diagnosis of mental subnormality, because most (but not all) severely subnormal infants show progressive microcephaly, the curve of successive head circumference measurements falling further and further away from the mean. The continued average rate of increase of head circumference would make one particularly careful about giving a gloomy prognosis. I believe that this unexpected improvement is more apt to occur in infants who suffered severe birth trauma than in others. It may be that the well-recognized difficulty of assessing the developmental potential of infants with kernicterus and other forms of athetosis may be related in part to this delay in maturation. Taylor[16] described children with athetosis who displayed maturational delay.

It would be useful if one could define the age period in which improvement in per-

formance can occur, and beyond which no improvement can be expected. I cannot do this. In most of the infants whom I have observed, improvement was obvious by the age of 4 or 5 months. Other children, however, remained retarded for a much longer period (e.g. Case 1) and yet achieved a superior I.Q. score later. Patient 5 was thought by another doctor to be mentally defective at the age of 17 months, and she was indeed seriously retarded at that age, but her last I.Q. score was 118.

One imagines that teachers have frequently seen children who showed late maturation in their school work. Numerous eminent persons were backward at school; Einstein showed no talent in his school work; others included Tolstoy, Thomas Chatterton, Rossini, Thackeray, Mirabeau, Robert Clive, John Hunter, Anthony Trollope, James Watt, Isaac Newton, the Duke of Wellington, Sheridan, Oliver Goldsmith, and Winston Churchill, to mention just a few. It may well be that the reason for backwardness in some lay in poor teaching, and that the marks of genius were there but were not recognized. In others the backwardness may have been due to delayed maturation. When a child makes poor progress at school, the commonest cause is a subnormal level of intelligence. One must always remember, however, that there are many other causes of defective progress at school, one of which is delayed maturation with an average or better than average intellectual potential.

True examples of delayed maturation in all fields are not common. Their frequency is apt to be exaggerated. It is true, however, that one is much more likely to underestimate an infant's or child's ability than to overestimate it, and the possibility of unexpected improvement must always be remembered.

DELAYED MOTOR DEVELOPMENT

Mental subnormality is the commonest cause of delayed motor development in a child who is also retarded in all other aspects of development. Severe emotional deprivation may also retard a child in this and other aspects of development.

When a child shows delay in gross motor development and yet is up to the average in other aspects of development, the commonest cause is a mechanical difficulty involving hypotonia or hypertonia. Hypotonia is readily diagnosed by the feel of the muscles, by passive movement of joints, by assessing the range of movement of joints, and by "shaking" the limb and noting the movement of the hands or feet. Minor degrees of cerebral palsy, however, can readily be missed in infancy, and I have myself diagnosed isolated motor retardation, only to find by the time the child is 3 years of age that the true diagnosis was spastic paraplegia of mild degree. The motor retardation sometimes seen in athetoid children, before the characteristic athetoid movements are found, is particularly confusing. There remain, however, children with notable delay in motor development who on follow-up examination have no mechanical disability. I am not sure whether gross obesity delays walking or not, but obesity was not a feature of any of the children to be described, and all on follow-up examination at school were normal in all respects. Extreme degrees of delayed motor maturation are rare, but I have seen 8 children who had a normal level of intelligence and who had no mechanical disability, but who were unable to walk unsupported until after the second birthday.

Case 16. This boy was born normally at term. I was able to follow him from birth to school age. He was normal in the newborn period. He began to smile at 6 weeks, to vocalize with smiles at 8 weeks, to chew, transfer, and roll from prone to supine at 6 months, to say words with meaning at 8 months, to release objects and play patacake at 11 months, to put words together at 15 months, and to feed himself, managing a cup, at 18 months—all average or better than average in performance. The acquisition of head control was grossly retarded, and he could not sit for seconds without support until 19 months or walk without support until 30 months. There was no mechanical

disability. His I.Q. test score at the age of 5 years was 104.*

Case 17. This girl was born normally at term, and was well in the newborn period. She was average in all aspects of development, except in gross motor skills. She was able to get hold of objects by 6 months and to say words with meaning at 12 months. But she could not sit unsupported until 12 months or walk alone until 3 years. There was no mechanical disability. At the age of 17 years she was able to dance normally and play hockey, and was top of her class at a technical college.

The other children were unable to sit until the age of 12 months or later, and with the exception of one child who could not walk alone until 4 years, all were able to walk between 24 and 30 months. All were free from a mechanical disability, and all proved to have a normal level of intelligence. There was a history of late walking in the father of one child.

It is quite possible that some of these cases represented extremely mild forms of cerebral palsy or were examples of "minimal birth injury" as described by Gesell and associates.[5] Case 17 was thought possibly to fall into the latter category. At the technical school (in adolescence) there was a suggestion of clumsiness of movement, and she could type only 50 words a minute. Case 5 was thought possibly to be an example of minimal birth injury. Though apparently normal in later years she was never really nimble on her feet, though there were no definite signs of abnormality.

Some apparently normal children are more clumsy than others, in fine or gross motor skills. Some authorities have termed them "motor morons." Ford[3] uses the more elegant term "congenital maladroitness."

The more carefully one examines the newborn baby, using the methods of Peiper, Prechtl, and André Thomas, the more frequently one finds infants who show abnormal neurological signs in the newborn period and yet reach normality or near-normality later.

*Institute of Education, the University of Sheffield.

DELAYED SPHINCTER CONTROL

The commonest cause of delay in acquiring clean habits is mental subnormality. Though there are still psychiatrists who claim that all or most examples of enuresis are psychological in origin, I am convinced that the majority of cases of children who have never been dry (i.e., who have not developed enuresis after a "dry" phase) and who are normal mentally are best explained on an organic basis. It is obvious that bed-wetting may lead to psychological problems, but I do not think that parental mismanagement of "training" or insecurity in the child is more than an unusual cause of the problem. In nearly all these children there is a family history of the same complaint. There was a history of bed-wetting in immediate relatives of 18 of the last 20 consecutive, school-age children who have never been dry from birth.

Muellner[10] described the complex series of stages through which the child has to pass before he acquires full control of the bladder. He has to progress from the stage of the automatic emptying of the bladder to awareness of the full bladder, to learning to inhibit the contraction of the detrusor muscle and to hold the urine through the use of the levator ani and the pubococcygeus, to the stage when he can control the intra-abdominal pressure through the use of the diaphragm and abdominal muscles, and to the final stage when he can start and stop the flow of urine at any degree of bladder filling.

SPEECH

I have discussed the problem of delay in speech elsewhere.[6]

When one has excluded the obvious causes of delayed speech development, such as mental subnormality, deafness, and cerebral palsy, there remains a considerable group of children with an average or superior level of intelligence who are late in learning to speak. Einstein occasioned considerable anxiety with regard to his mental development when he had reached 4 years of age and was unable to speak properly. There is frequently a

family history of lateness of speech. Sometimes there is no discoverable cause. Delayed maturation in the centers and pathways concerned may well be the usual cause.

HEARING

The commonest cause of delayed auditory maturation is mental subnormality. One frequently sees infants who are suspected of being deaf, but who are found to be retarded in other fields of development. A full examination is obviously essential in order to assess the child's general level of development and to relate this to his hearing responses. It may well be that some mentally subnormal infants are relatively more retarded in hearing development than in other fields, but further study is necessary to provide convincing evidence of this.

There is evidence that delayed auditory development occurs in otherwise normal infants. In these, it may be termed developmental auditory imperception or developmental auditory agnosia.

Dr. Mary Sheridan[14] states that she has seen several normal children with delayed maturation of hearing and others with delay in learning to localize sound. Dr. Murphy of Reading[11] states that delayed maturation in the auditory mechanism is not uncommon. He wrote that one child, the son of deaf parents (the mother probably having congenital deafness), made no reaction to any sound up to the age of 6 months. He was being treated as deaf at this age when he not only began to react to sound but developed the ability to localize sound, like an 8-month-old infant. Dr. Murphy wrote that he has seen fairly often infants of 4 or 5 months of age who temporarily inhibit the reaction to sound after the first mild response, thus giving the impression of deafness. In order to obtain a reliable picture of their ability to localize sounds it was essential to use a very large number of sounds varying in frequency and significance. Dr. Murphy pointed out that mechanical causes of defective hearing, such as wax in the ear and adenoidal obstruction of the eustachian tube, must always be eliminated before delayed auditory maturation can be diagnosed. It should also be remembered that gross emotional deprivation may so reduce a child's responsiveness that he may seem to have defective hearing.

Dr. Ingram[8] of Edinburgh wrote that he has studied many cases of delayed auditory maturation. He suggested that in one group, comprising children with kernicterus, especially, there may be prenatal damage to the auditory nerve or its connections, followed by some recovery. He wrote that children with kernicterus may fail to react to sound at all for a period after birth and then begin to react at 4 or 5 months of age. He considered that there is a second group, with cerebral agnosia, some of them associated with brain damage. They appear to be deaf for some months, and they then begin to respond. They are likely to show a delayed ability to discriminate between the sounds in their environment and to localize sounds. They are late in learning to distinguish between the voices of their parents and of their siblings and in learning to perceive and distinguish what is said, so that speech is delayed. In those without evidence of brain damage there is often a family history of delayed speech, specific reading disability, and of delay in the establishment of handedness. Ingram felt that in some mentally subnormal children the delay in responding normally to sound is greater than the general level of development would lead one to expect; the delayed auditory maturation is of greater degree than the delay in other fields.

VISION

I have described the problem of delayed visual maturation elsewhere.[7] I described 2 children who appeared to be blind for the first few weeks, though average in all other aspects of development. They began to show signs of vision at the age of about 6 months, and eventually had normal eyesight.

PSYCHONEUROLOGICAL PROBLEMS

This group of problems has been the subject of considerable discussion in recent years

because of the recognition of the frequency with which they occur in children with cerebral palsy and children who suffered "brain injury" in utero or subsequently (Strauss and Lehtinen,[15] Albitreccia,[1] Forward,[4] and Walton[17]). The term, "psychoneurological learning disorders," was used by Mykelbust and Boshes[12] in a valuable review of such difficulties as apraxia, agnosia, dysgraphia, dyslexia, and dyscalculia. They suggested that more than 5 per cent of the American public school population may have these problems.

The perceptual errors in children with cerebral palsy may be due partly to organic brain defects but, also, partly to lack of experience which in turn may be related to their sensory handicaps, such as impaired vision or hearing, their difficulties in speech and kinesthetic sense, or to their mechanical disabilities, making it impossible for them to obtain tactile experience like other children because they cannot grasp and feel objects.

Many of the features of the perceptual problems of children with cerebral palsy are identical with those of normal younger children, thus suggesting that delayed maturation is a factor, though this may be related in part to environmental difficulties. For instance, features common to both normal young children and older children with psychoneurological problems are reversal of symbols (interpreting p as d); reversal of words and reading from right to left (interpreting TUB as BUT and 369 as 963); the difficulty of distinguishing right from left; the difficulty in space appreciation and body image (as seen in the difficulty of putting on a cardigan—the young child putting it on back to front and inside out); the difficulty with the form board; and the difficulty in placing cut-out cardboard, lip, nose, eyes, and ears on an empty "head."

Another point in favor of the theory that delayed maturation may be one cause of the psychoneurological problems of children with cerebral palsy is the fact that these problems become less frequent with increasing age.

The problem of dyslexia, a specific reading disability, is a big one which is by no means completely understood. The relationship of dyslexia (and of delay in acquiring speech) to delay in the establishment (and, therefore, maturation) of laterality is uncertain. In all children with dyslexia, as with delay in other aspects of development, it is essential to relate the level reached to the general level of development. When the retardation in reading is out of all proportion to the general retardation, as shown by the I.Q. test score, one is justified in diagnosing specific reading disability and attempting to help the child by remedial teaching by the specific methods normally used.

It seems that Dr. John Hunter had a specific reading disability. Despite the efforts of teachers and relatives, he was unable to read until he was 17 years old, and, in consequence, his school performance was very poor.

It may be that difficulties with other subjects at school can be explained in some cases on the same basis. Innumerable children have difficulty with mathematics and it is thought by some that the subject is taught too soon. Napoleon throughout his life had difficulty in spelling and writing. Charles Darwin, Thackeray, and the Duke of Wellington experienced difficulty with languages.

PSYCHOLOGICAL IMMATURITY

Psychological immaturity is so well recognized that it is unnecessary to devote further space to it. It is obvious that environmental factors, such as overprotection or emotional deprivation, play a large part in its causation, but developmental factors may also be relevant.

Schizophrenia and autism may be to some extent problems of delayed maturation, or at least of failure of maturation.

DISCUSSION

In developmental assessment it is essential not only to be thoroughly conversant with the normal, but also to be fully aware of normal variations. Developmental prediction is at all times difficult because all children are different, different in their intellectual potential, in their pattern of development,

and in the environment which they meet. Many are now interested in the reason for different patterns of development, and in this paper I have discussed one of these—delayed maturation of parts of the nervous system. It is inevitable that the argument is based on deductive reasoning rather than on histologic evidence.

It has long been recognized that some children are "slow starters." It is essential to remember that some infants are seriously retarded in the early weeks and yet may catch up to the average or prove to have a better than average level of intelligence. This unexpected improvement is rare, but failure to recognize the possibility may lead to the serious error of diagnosing mental subnormality in a normal child. In the assessment of children for the purpose of adoption it is particularly important to be guarded about the prognosis if an infant is backward, particularly if there have been emotional deprivations. Repeated examinations, in order to assess the rate of development, are essential. The occurrence of these examples of delayed maturation well illustrates the serious mistake of diagnosing mental subnormality too readily and, in particular, of diagnosing it by clinical impression instead of by careful history taking, physical and developmental examination, careful interpretation of one's findings, and follow-up studies.

Delayed maturation which causes backwardness at school is of the greatest importance. This may consist of general backwardness, or backwardness in certain aspects of development, such as speech, reading, and psychoneurological learning disorders. Once more, the great danger is that of diagnosing mental subnormality or failing to recognize mental superiority. As in infancy, when a child is backward at school in one or all subjects, the reason for the backwardness should be sought, because the backwardness may be remediable. These difficulties should be a subject of collaboration between the pediatrician, psychologist, and teacher.

Delayed visual and auditory maturation may lead not only to the diagnosis of mental subnormality but to the incorrect diagnosis of blindness or deafness. Delayed sphincter control may lead to unnecessary psychiatric treatment for a condition which is primarily organic.

The role of remedial teaching in delayed maturation is uncertain and requires further study. For instance, if a child with severe psychoneurological learning disorders, of the type described by Walton,[17] slowly and painfully learns to master his difficulties after years of intensive training by devoted psychologists, it is not easy to prove that the improvement is the result of the training and not the result of maturation of the nervous system. Many efforts were made to teach Dr. John Hunter to read, but the fact that he learnt at the age of 17 did not seem to be the result of his teaching, as far as one can tell from his biography.[13] There is much yet to be learnt about the problem.

SUMMARY

The possibility of delayed maturation must always be remembered in developmental assessment. An infant may be seriously retarded in early weeks and yet achieve an average or superior I.Q. test score in later years, without mechanical disability. Such delayed maturation is rare but important, because it may lead to the wrong diagnosis of mental subnormality. Delayed maturation may continue into school years.

Delayed maturation occurs in individual aspects of development in otherwise normal children. It may involve delayed visual or auditory responses, delayed sphincter control, and psychoneurological difficulties.

REFERENCES

1. Albitreccia, S. I.: Recognition and Treatment of Disturbances of the Body Image, Cerebral Palsy Bull. Vol. 1, No. 4, p. 12, 1958.
2. Dekaban, A.: Neurology of Infancy, London, 1959, Baillière, Tindall & Cox.
3. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence, Oxford, 1960, Blackwell Scientific Publications.
4. Forward, C. E.: The Treatment of Defective Children, Occup. Therapy, July, 1959, p. 11.
5. Gesell, A., Amatruda, C. S., Castner, B. M., and Thompson, H.: Biographies of Child Development, London, 1939, Hamish Hamilton.

6. Illingworth, R. S.: The Development of the Infant and Young Child; Normal and Abnormal, Edinburgh, 1960, E. & S. Livingstone, Ltd.
7. Illingworth, R. S.: Delayed Visual Maturation, Arch. Dis. Childhood (in press).
8. Ingram, T. T. S.: Personal communication, 1961.
9. Macdonald, M. S., and Emery, J. L.: The Late Intrauterine and Postnatal Development of Human Renal Glomeruli, J. Anat. **93:** 331, 1959.
10. Muellner, S. R.: Development of Urinary Control in Children, J. A. M. A. **172:** 1256, 1960.
11. Murphy, K. P.: Personal communication, 1961.
12. Mykelbust, H. R., and Boshes, B.: Psychoneurological Learning Disorders in Children, Arch. Pediat. **77:** 247, 1960.
13. Paget, S.: Life of John Hunter, London, 1897, Fisher Unwin.
14. Sheridan, A.: Personal communication, 1961.
15. Strauss, A. A., and Lehtinen, L. E.: Psychopathology and Education of the Brain Injured Child, New York, 1948, Grune & Stratton, Inc.
16. Taylor, E. M.: Psychological Appraisal of Children With Cerebral Defects, Cambridge, 1959, Harvard University Press.
17. Walton, J. N.: Clumsy Children, Spastics Quarterly **10:** 9, 1961.

Mycobacterial cervical adenitis in children

Starkey D. Davis, M.D., and George W. Comstock, M.D.*

COLUMBUS, GA.

CAREFUL quantitative studies in different parts of the world have made it obvious that tuberculin sensitivity must often result from infections with some organism other than *Mycobacterium tuberculosis*.[1] Acceptance of this conclusion has naturally led to a search both for organisms which might be responsible for nonspecific tuberculin sensitivity and for diseases which might follow upon such infections. At present, two mycobacteria (the "yellow bacillus" and the "Battey bacillus") have been implicated as important causes of human disease and tuberculin sensitivity,[2-6] other mycobacteria are under careful study as possible causes,[7-9] and others may yet be found. Although most disease attributed to these newly recognized "atypical" myobacteria has resembled pulmonary tuberculosis, chronic cervical adenitis has also been reported.[10-14] The close resemblance to scrofula makes clinical differentiation almost impossible, with the result that many cases must masquerade as tuberculosis. To obtain some indication of the etiological importance of atypical mycobacteria, all cases of mycobacterial cervical adenitis in children known to the Muscogee County Tuberculosis Study have been investigated and form the basis for this report.

From the Tuberculosis Program, Division of Special Health Services, Public Health Service, United States Department of Health, Education, and Welfare, Washington 25, D. C.

**Address, Tuberculosis Program, Washington Office, CDC, Public Health Service, Washington 25, D. C.*

MATERIAL AND METHODS

The Muscogee County Tuberculosis Study was established in Columbus, Georgia, in May, 1946, as a research facility supported by the Muscogee County Health Department, the Georgia State Health Department, and the United States Public Health Service. A very close working relationship has been maintained with the Health Department of adjacent Russell County, Alabama, and the medical profession of the Columbus area, including Fort Benning, Georgia. Because of local cooperation and interest, it is believed that nearly all definite or suspected cases of active tuberculosis are known to the Study.

A search of Study records disclosed 24 cases of cervical adenitis which met the following criteria: (1) the adenitis was clinically compatible with a diagnosis of tuberculosis; (2) the patient was less than 12 years old when the disease was first noticed; and (3) the onset occurred between May 1, 1946, and July 1, 1960. Twenty-two of the 24 children lived at some time during this period in the metropolitan area of Columbus, which includes Muscogee, Russell, and Chattahoochee Counties as well as Fort Benning, a large Army post. The other 2 patients lived in adjacent counties in Alabama and Georgia. Although an appropriate base population for these cases is not available, an indication of its size is afforded by the 1950 Census which showed about 43,000 children under 12 years of age in the metropolitan area.

All cases were routinely tuberculin tested with 0.0001 mg. of PPD-S prepared from a strain of *Myco. tuberculosis*. When PPD-B prepared from the Battey strain of atypical mycobacteria became available, patients still residing in the area or subsequently reported were tested with 0.0001 mg. of that antigen. In the spring of 1960, PPD-G was prepared from a scotochromogenic mycobacterium isolated from one of the children in this series (Case 14). All children who could be reached were then tested with 0.0001 mg. of PPD-G together with a similar dose of PPD-S and PPD-B.* Whenever more than one antigen was given, a scheme of administration was used that prevented the reader from knowing which test had been read until the measurements for all of them had been recorded. Only the most recent tests on each patient are considered in this report.

The etiological classification of these cases would have been simpler if an organism had been isolated and identified from a node of every patient. Unfortunately, this was not possible. Seven children had no sinus tract drainage during the time they were known to the Study and their physicians did not advise surgical excision. Of the other 17, bacteriologic examinations were made on 14, but the cultures were positive in only 11. Furthermore, some organisms were isolated before it was possible to perform the currently recommended tests for identification. Thus the bacteriologic classification used in this report is based on inspection of gross colony characteristics, the demonstration that the colonies were composed of acid-fast bacilli, and, in recent years, the results of the niacin test. These procedures, while insufficient to classify atypical mycobacteria, probably separate them from *Myco. tuberculosis* as reliably as is possible at present in a general bacteriologic laboratory.

For patients without a bacteriologic diagnosis, the pattern of skin sensitivity to the mycobacterial antigens was accepted as the criterion for classification. This decision was based on the demonstration by others that the antigen prepared from the mycobacterium with which guinea pigs were infected caused larger reactions than other mycobacterial antigens.[7] Thus, if the reaction to PPD-S was larger than reactions to PPD-B and PPD-G, the etiological agent was considered to be *Myco. tuberculosis*. Conversely, if the reaction to PPD-B or PPD-G was clearly larger, *Myco. tuberculosis* was considered unlikely to be the cause of the disease. Patients with essentially equal reactions to all three antigens may well be infected with more than one type of organism. They were arbitrarily assigned to the group with *Myco. tuberculosis* as the probable etiological agent even though it is believed that this procedure tends to overstate the size of this segment. For the sake of simplicity, the two groups will be called the "tuberculous group" and the "atypical group."

It should be mentioned that no other cause for cervical adenitis was found in any of the 24 patients, and that all excised nodes showed granulomatous changes on histologic examination.

RESULTS

A summary of the findings in the 24 children is given in Table I. In half of them, the onset of the illness was in the last 2½ years of the 14 year period. This concentration of cases in the last few years probably resulted from better recognition and reporting associated with recent interest in atypical mycobacteria. When their disease developed, 19 of the children were living in the Columbus metropolitan area, 3 were living elsewhere in Georgia and Alabama, while 1 each developed the disease in Kansas and Puerto Rico.

Seven children were assigned to the tuberculous group. Organisms with the gross colony characteristics of *Myco. tuberculosis* were isolated from the nodes of 2 children; the other 5 all had reactions to PPD-S which were larger than or essentially equal to the reactions to PPD-B or PPD-G. However, in

*The PPD-S used in this study was the international standard PPD prepared by Dr. Florence Seibert. PPD-B and PPD-G were prepared like PPD-S by Dr. Lewis Affronti under Dr. Seibert's direction. The dosage for each antigen is expressed as milligrams of protein.

only 1 of the 7 was the reaction to PPD-S clearly largest.

A particularly awkward problem in classification arose with Case 6, in which the skin test and bacteriologic results were in disagreement. This child was tested with PPD-S and various mycobacterial antigens on 4 separate occasions. PPD-S never caused any induration, and PPD-B always caused the largest reactions. The bacteriologic findings seem equally conclusive in the opposite direction, however. On the day a node from this patient was cultured in the laboratory, no other examinations for acid-fast bacilli were done. Colonies apparently typical of *Myco. tuberculosis* grew on each of the 4 culture tubes that were inoculated. Although this organism is still being studied, 4 laboratories have expressed the opinion that it is probably *Myco. tuberculosis* and the case has been classified as tuberculous in this report.

Seventeen children were classified as having disease caused by one of the atypical mycobacteria. Acid-fast bacilli were demonstrated in 10 of 13 attempts, once only on a stained section of a node and once on a culture which was reported only as "positive for acid-fast bacilli" by another laboratory. The remaining 8 all showed small smooth colonies. For 2 subjects, the colonies were cream colored, while for 6 they were orange or yellow. None of the atypical group showed much sensitivity to PPD-S. Only 4 children had reactions to PPD-S measuring 6 mm. or more in diameter, and all were less than 10 mm. Sixteen cases were tested with PPD-B and 13 had reactions of 6 mm. or more. Of the 16 cases tested with PPD-G, 15 reacted to this antigen, 14 having larger reactions to PPD-G than those to PPD-S or PPD-B.

In this group, Case 9 presents a problem in classification. No organisms were demonstrated in the sinus tract drainage, possibly because treatment had been started before a specimen was cultured. Furthermore, the results of the most recent skin tests are not impressive; no induration at all was caused by PPD-S and PPD-B, and only 2 mm. by PPD-G. However, while PPD-S had similarly caused no reaction a year earlier, PPD-B at that time had resulted in an induration measuring 10 mm. It is difficult to interpret these findings. Perhaps the etiological agent in this case is not closely related antigenically to any of the 3 PPDs used in this study; another possibility is that sensitivity evoked by some of the atypical mycobacteria may be more evanescent than that caused by *Myco. tuberculosis.*

The tuberculous group differed considerably in some clinical features from the atypical group. Among the 7 children in the tuberculous group, 6 were Negroes and 5 were males. This represents a clear excess of Negroes and a slight excess of males when compared with the general population. The tuberculous group also contained the only 2 children with a history of prolonged household exposure to tuberculosis. The onset of cervical adenopathy in all of the tuberculous children was associated with no other symptoms even though 6 of them had lesions elsewhere. Four had definite and 1 possible enlargement of the hilar nodes. The other child had involvement of both axillary and mediastinal nodes. One child with hilar adenopathy had had the diagnosis of primary pulmonary tuberculosis 6 months prior to the onset of her cervical adenitis. The pulmonary disease was treated with streptomycin for 2 months and had almost completely cleared when enlargement of a cervical node was noted.

Among the 17 children in the atypical group, the racial composition was essentially the same as that of the general population, with 12 whites and 5 Negroes. Eleven of the 17 were females. Only 1 child had a history of contact with tuberculosis, having been exposed for only 10 days to a relative visiting in the home. In 5 of the atypical cases, the onset was accompanied by fever and evidence of upper respiratory infection. Associated lesions were noted in only 1 child, who was observed to have enlarged hilar nodes at the initial examination.

In other respects, the two groups were quite similar. Three children in each group had rural addresses when their disease was

Table I

Case No.	*Race*	*Sex*	*Onset of illness*			*Associated lesions*	*Sinus tract*	*TB contact*
			Date	*Age in months*	*Residence*			
Tuberculous group								
1	W	M	7/58	25	Ft. Benning, Ga.	Axillary and mediastinal nodes	Yes	No
2	N	M	1/53	9	Talbot Co., Ga.	Hilar nodes	Yes	Yes
3	N	M	6/56	21	Muscogee Co., Ga.		No	No
4	N	M	7/52	33	Muscogee Co., Ga.	Hilar nodes	Yes	No
5	N	M	11/54	86	Muscogee Co., Ga.	Hilar nodes	Yes	No
6	N	F	9/59	22	Muscogee Co., Ga.	Hilar nodes?	No	No
7	N	F	4/51	80	Muscogee Co., Ga.	Primary pulmonary tuberculosis	No	Yes
Atypical group								
8	W	M	10/58	18	Coffee Co., Ga.		Yes	No
9	W	M	7/58	28	Muscogee Co., Ga.		Yes	No
10	W	M	8/57	29	Puerto Rico		Yes	No
11	W	M	4/58	30	Muscogee Co., Ga.		No	Yes
12	W	M	1/52	44	Muscogee Co., Ga.		Yes	No
13	W	F	7/59	10	Lee Co., Ala.		No	No
14	W	F	9/57	17	Russell Co., Ala.		Yes	No
15	W	F	11/49	18	Kansas		Yes	No
16	W	F	5/59	20	Muscogee Co., Ga.		No	No
17	W	F	3/50	23	Muscogee Co., Ga.		Yes	No
18	W	F	3/59	26	Ft. Benning, Ga.	Hilar nodes	No	No
19	W	F	6/46	31	Muscogee Co., Ga.		Yes	No
20	N	M	11/54	129	Muscogee Co., Ga.		Yes	No
21	N	F	4/60	15	Muscogee Co., Ga.		No	No
22	N	F	5/60	17	Russell Co., Ala.		No	No
23	N	F	12/58	21	Muscogee Co., Ga.		No	No
24	N	F	11/58	27	Chattahoochee Co., Ga.		Yes	No

Induration to 0.0001 mg. PPD (mm.)			Bacteriologic findings	Treatment				Outcome
					Chemotherapy			
S	B	G		Surgical	Drugs	Months	Continuing	
11	9	12			INH and PAS	18	Yes	Well 6 mo., 7/60
					SM also	1		
19	12	10			SM and PAS	9	No	Well 7 yr., 7/60
					INH and PAS	14		
10	13	11	Rough, buff colonies	Incision and drainage	INH and PAS	6	No	Well 3½ yr., 7/60
30	25	24		Incision and drainage				Well 8 yr., 7/60
19	12	17			Prophylaxis study	12	No	Well 4½ yr., 7/60
0	15	12	Rough, buff colonies	Excision	SM and PAS	2	Yes	Well 8 mo., 7/60
					INH and PAS	7		
21	18	12			SM	2	No	Well 9 yr., 7/60
0	9	13	Culture neg.	Incision and drainage	INH	12	No	Well 1½ yr., 9/60
0	0	2	Culture neg.		INH and PAS	8	Yes	Slight drainage, 8/60
					SM and PAS	5		
					INH and PAS	10		
7	13	18	Smooth, cream-colored colonies	Excision	SM, INH, and PAS for recurrence	7	No	Recurrence 2 yr., later treated by excision. Well 7 mo., 7/60
3	7	16	Sections neg. for acid-fast bacilli	Excision	INH	12	No	Well 2 yr., 8/60
3			Smooth, orange-yellow colonies	Incision and drainage	SM	1	No	Well 8 yr., 7/60
8	14	15	Smooth, orange colonies	Excision	SM and INH	3	No	Well 9 mo., 7/60
0	10	18	Smooth, orange colonies	Incision and drainage	INH	12	No	Well 2 yr., 7/60
0	16	22		Incision and drainage				Well 9½ yr., 9/60
3	11	15	Sections pos. for acid-fast bacilli	Excision	INH and PAS	2	No	Well 1 yr., 7/60
			Culture neg.		SM and PAS	12		
0	4	12		Incision and drainage	SM and PAS	3	No	Recurrence 1½ yr., later treated by excision. Well 7 yr., 7/60
6	10	13	Smooth, cream-colored colonies	Excision	INH and PAS	2	Yes	Recurrence 1 yr., later treated by incision and drainage. Well 5 mo., 9/60
					INH	16		
5	12	16		Incision and drainage				Recurrence 5 yr., later not treated. Well 8½ yr., 7/60
0	8	12	"Culture pos. for acid-fast bacilli"	Incision and drainage	SM and PAS	2	No	Well 5 yr., 7/60
0	3	8	Smooth, yellow colonies	Aspiration	SM and PAS	3	Yes	Well 1 mo., 7/60
8	20	16	Smooth, orange-yellow colonies	Excision	SM and INH	1	Yes	Well 1 mo., 8/60
3	15	16	Smooth, orange-yellow colonies	Excision	SM and PAS	6	No	Well 1½ yr., 7/60
0	6	19						Well 7 mo., 7/60

first noted. Almost all patients were between the ages of 1 and 3 years at onset, only 1 in each group being younger and 2 in each group being older. No child in either group has shown evidence of granulomatous disease other than that indicated in the table.

Almost all cases were treated, with no significant differences between the two groups in the type of treatment administered. Eighteen were operated upon. The node was excised initially in 8 cases, incised and drained in 9, and aspirated in 1. Chemotherapy—streptomycin, para-aminosalicylic acid, or isoniazid, either singly or in combination—was given to 19 children. One child was placed in a controlled trial of isoniazid as a prophylactic agent against miliary and meningeal tuberculosis. He received tablets for 1 year, but it is not known whether these were isoniazid or placebo. Only 1 patient received no treatment of any kind.

All children were living and well at last report, although 6 were still under treatment. Draining sinuses, either spontaneous or postoperative, occurred in about 60 per cent of both groups. Sinuses which followed incision and drainage were not counted unless they persisted for at least 1 month. The likelihood of developing a sinus tract appeared to be related to the type of therapy. Five of 6 patients who received no surgical treatment and 8 of 9 who had incision and drainage developed draining sinuses, while only 1 of 8 with excision of the node had this complication. Chemotherapy apparently helped prevent the formation of a sinus. Only 9 of 19 patients with chemotherapy, but all 4 patients without any chemotherapy, developed sinuses. There was no indication in this small series that any drug regimen was superior to the others.

DISCUSSION

In this community in the southeastern United States, it appears that most cases of granulomatous cervical adenitis in children are not caused by *Myco. tuberculosis*. Even when cases of doubtful etiology are assigned to the tuberculous group, 70 per cent of the cases were classified as being caused by atypical mycobacteria.

While this disease is not rare, neither does it appear to be common. Only 8 cases are known to have occurred in the metropolitan area of Columbus, Georgia, in the past 2½ years, yielding an estimated incidence of less than 5 cases per 100,000 children per year. However, the group at risk can be more sharply defined as children between 1 and 3 years of age who react to PPD-G. Small-scale testing of pre-school children in Muscogee County during the summer of 1960 suggests that about 6 per cent of this age group react to PPD-G.[15] Since there were undoubtedly more than 10,000 children of this age in the metropolitan area, the annual attack rate among 1- and 2-year-old children reacting to PPD-G cannot be more than 0.5 per cent.

Differentiation of cervical adenitis caused by *Myco. tuberculosis* from that caused by other mycobacteria is not easy. A history of exposure to tuberculosis, the onset of cervical node swelling without fever or upper respiratory infection, and the presence of other lesions appear to favor the diagnosis of typical tuberculous disease in this and another recently reported series.[10] Tuberculin tests with 0.0001 mg. of PPD-S will almost always be positive in cases of tuberculous disease, but may often be negative in atypical cases. The results in this series suggest that dual testing, using both PPD-S and an antigen prepared from one of the atypical mycobacteria responsible for cervical adenitis, may be helpful in establishing the etiology. The bacteriologic examination, while undoubtedly the most reliable method of diagnosing mycobacterial adenitis, is much less satisfactory in identifying the particular mycobacterium involved. The separation of *Myco. tuberculosis* from the atypical mycobacteria appears to be fairly clear-cut, but differentiation of atypical strains is still tentative.[9]

The results of treatment in this series suggest that both surgical and medical treatment may be indicated. Of the surgical procedures, excision gave better results than incision and drainage. Not only was the

incidence of draining sinuses lower, but the most adequate specimen for bacteriologic examination was afforded by excision. Chemotherapy also appeared to reduce the likelihood of a draining sinus; the combination of choice appears to be streptomycin and isoniazid since most mycobacteria responsible for cervical adenitis are reported to be at least moderately susceptible to these drugs, while many of the atypical mycobacteria are resistant to PAS.[5, 16, 17] The chemotherapeutic regimen should be changed, if necessary, when the results of drug susceptibility tests are reported. Although the optimum duration of treatment is not known, it would seem wise to continue medication for at least a year.

Except for the tendency to develop draining sinuses, the prognosis of cervical adenitis caused by atypical mycobacteria appears to be good, and apparently better than that for typical tuberculous scrofula. If subsequent experience confirms this impression, the relative frequency of atypical cases might be related to the validity of Marfan's law, which states that children whose scrofula heals before adolescence are unlikely to develop tuberculosis in later life.[18] This dictum was confirmed by the experience in one series of cases in Maryland[19] but denied by authors from Massachusetts and Minnesota.[20, 21] Although the frequency of atypical mycobacterial infections in these areas is not known, the results of testing with PPD-B are consistent with the possibility that atypical infections are more common in Maryland than in the other two states.[3, 22]

In the future, as infection with *Myco. tuberculosis* continues to diminish, atypical mycobacteria will undoubtedly be responsible for an increasing proportion of cases of chronic cervical adenitis. Tuberculin tests with PPD-S alone, while helping to rule out tuberculous infection, will be of little assistance in the differential diagnosis of atypical mycobacterial disease from other forms of adenitis. Until a suitable diagnostic test is generally available, it seems advisable to excise all cervical nodes which are chronically enlarged without obvious cause. Not only does this procedure afford the best opportunity for pathologic and bacteriologic diagnosis, but for mycobacterial cervical adenitis it also appears to be good treatment.

SUMMARY

Since May 1, 1946, 24 cases of mycobacterial cervical adenitis in children under the age of 12 years were reported to the Muscogee County Tuberculosis Study. It is believed that these represent practically all the known cases in the community. On the basis of bacteriologic findings and skin sensitivity to PPD-S and other mycobacterial antigens, the cases were separated into 2 groups: one in which *Myco. tuberculosis* was a likely etiological agent, and the other in which the disease was probably caused by some other mycobacterium.

In this series, it appeared that most cervical adenitis, clinically compatible with a diagnosis of tuberculosis, was caused by mycobacteria other than *Myco. tuberculosis*. A history of exposure to tuberculosis, an insidious onset in a male Negro child, and the presence of lesions elsewhere in the body favored the diagnosis of tuberculosis. Dual skin testing, with the use of PPD-S and a PPD prepared from an atypical acid-fast bacillus causing cervical adenitis, appeared to be helpful in differentiating tuberculosis from other mycobacterial cervical adenitis. Bacteriologic examinations afforded the best opportunity to obtain an etiological diagnosis.

The treatment of choice appeared to be excision of the affected node, accompanied by antituberculosis chemotherapy. Excision not only gave good therapeutic results in this series, but also yielded the best specimen for bacteriologic examination.

We wish to thank the following physicians for their assistance and for permission to publish the findings from their cases: the staff of the Pediatric Service, Martin Army Hospital, Ft. Benning, Georgia (Cases 1, 8, 9, 10, 16, 21); the staff of the Pediatric Service, The Medical Center, Columbus, Georgia (Cases 2, 6, 20, 23); Dr. Mercer Blanchard (Cases 14, 19); Dr. Mercer C.

Blanchard (Case 4); Dr. Ivan R. Elder (Case 12); Dr. William R. Jones (Case 17); Dr. A. J. Kravtin (Cases 3, 5); Dr. James W. Rhea (Case 11); Dr. Walker P. Rivers, Jr. (Cases 15, 22); Dr. Ralph E. Tiller (Cases 13, 18); and Dr. Robert B. Tudor, Bismarck, North Dakota (Case 18).

We are also grateful to Maj. Glenn West, MC, pathologist at Martin Army Hospital, Ft. Benning, Georgia, for assistance in obtaining bacteriologic and pathologic examinations on the cases treated there. We particularly wish to thank Miss Martha Jane Spence, Director of Laboratories, Muscogee County Health Department, Columbus, Georgia, who was responsible for most of the original isolations and classification of the acid-fast bacilli obtained in this series.

REFERENCES

1. Edwards, P. Q., and Edwards, L. B.: Story of the Tuberculin Test From an Epidemiologic Viewpoint, Am. Rev. Resp. Dis. **81:** No. 1, Part 2, 1960.
2. Crow, H. E., King, C. T., Smith, C. E., Corpe, R. F., and Stergus, I.: A Limited Clinical, Pathologic, and Epidemiologic Study of Patients With Pulmonary Lesions Associated With Atypical Acid-Fast Bacilli in the Sputum, Am. Rev. Tuberc. **75:** 199, 1957.
3. Edwards, L. B., and Palmer, C. E.: Epidemiologic Studies of Tuberculin Sensitivity I. Preliminary Results With Purified Protein Derivatives Prepared From Atypical Acid-Fast Organisms, Am. J. Hyg. **68:** 213, 1958.
4. Hardy, A. V., Dunbar, F. P., Jeffries, M. B., Bond, J. O., and Lewis, A. G., Jr.: Bacteriological and Epidemiological Studies of Pulmonary Diseases Associated With Atypical Acid-Fast Bacilli, Am. J. Pub. Health **48:** 754, 1958.
5. Keltz, H., Colton, R., and Lester, W.: A Characterization of Atypical Acid-Fast Bacilli Obtained From Patients With Pulmonary Tuberculosis, Dis. Chest **34:** 368, 1958.
6. Wood, L. E., Buhler, V. B., and Pollak, A.: Human Infection With the "Yellow" Acid-Fast Bacillus. A Report of Fifteen Additional Cases, Am. Rev. Tuberc. **73:** 917, 1956.
7. Edwards, L. B., Palmer, C. E., Affronti, L. F., Hopwood, L., and Edwards, P. Q.: Epidemiologic Studies of Tuberculin Sensitivity II. Response to Experimental Infection With Mycobacteria Isolated From Human Sources, Am. J. Hyg. **71:** 218, 1960.
8. Linell, F., and Norden, A.: Mycobacterium Balnei. A New Acid-Fast Bacillus Occurring in Swimming Pools and Capable of Producing Skin Lesions in Humans, Acta tuberc. scandinav. Supp. 33, 1954.
9. Runyon, E. H.: The Differentiation of Anonymous (Atypical) Mycobacteria From Mammalian Tubercle Bacilli, Bull. Internat. Union Tuberc. **29:** 69, 1959.
10. Chapman, J. S., and Guy, L. R.: Scrofula Caused by Atypical Mycobacteria, Pediatrics **23:** 323, 1959.
11. Florence, H.: Atypical Acid-Fast (Chromogenic) Organisms Complicating Pulmonary Disease, Dis. Chest **30:** 250, 1956.
12. Prissick, F. H., and Masson, A. M.: Cervical Lymphadenitis in Children Caused by Chromogenic Mycobacteria, Canad. M. A. J. **75:** 798, 1956.
13. Runyon, E. H.: Anonymous Mycobacteria in Pulmonary Disease, M. Clin. North America **43:** 273, 1959.
14. Weed, L. A., Keith, H. M., and Needham, G. M.: Nontuberculous Acid-Fast Cervical Adenitis in Children, Proc. Staff Meet. Mayo Clin. **31:** 259, 1956.
15. Tuberculosis Program, Public Health Service: Unpublished material.
16. Wolinsky, E.: Chemotherapy and Pathology of Experimental Photochromogenic Mycobacterial Infections, Am. Rev. Resp. Dis. **80:** 522, 1959.
17. Wolinsky, E., Smith, M. M., and Steenken, W., Jr.: Drug Susceptibilities of 20 "Atypical" as Compared With 19 Selected Strains of Mycobacteria, Am. Rev. Tuberc. **76:** 497, 1957.
18. Marfan, A. B.: La Scrofule. Forme speciale de tuberculose, Paris méd. **91:** 129, 1934.
19. Bordley, J., III, and Baylor, J. W.: Prognosis in Cases of Tuberculosis of the Tonsils, Adenoids and Cervical Lymph Nodes, Bull. Johns Hopkins Hosp. **63:** 132, 1938.
20. Miller, R. H.: Tuberculosis of the Lymphatic System, New York, 1934, The Macmillan Co., p. 38.
21. Myers, J. A.: Tuberculosis Among Children and Adults, ed. 3, Springfield, Ill., 1951, Charles C Thomas, Publisher, p. 204.
22. Palmer, C. E., Edwards, L. B., Hopwood, L., and Edwards, P. Q.: Experimental and Epidemiologic Basis for the Interpretation of Tuberculin Sensitivity, J. PEDIAT. **55:** 413, 1959.

Unpredictability of antibody response of infants to injections of Salk poliomyelitis vaccine

Henry G. Cramblett, M.D.,* and Samuel J. Fomon, M.D.

WINSTON-SALEM, N. C.

THE RESPONSE of infants to antigenic stimulation is variable.[1-6] In part, this is due to the inability of the small infant to respond immunologically as do the older child and adult. The extent to which passively transferred antibodies interfere with active immunization with living or dead poliovirus vaccines is not clear.[1, 6-8]

The present study was undertaken to obtain more information about the response of infants to antigenic stimulation with poliomyelitis vaccine and the influence of passively transferred antibodies. Serial determinations of antibody titers against the three types of poliovirus have been performed before, during, and after the course of inoculation of 45 normal, full-term infants with Salk vaccine.

SUBJECTS AND PLAN OF STUDY

For the most part, the infants in this study were the children of students at the State University of Iowa and infants who were being observed for other purposes in the Pediatric Metabolism Unit of the Department of Pediatrics, State University of Iowa. All except 2 of the mothers of these infants had received one or more injections of Salk vaccine. All inoculations were given by a registered nurse, and the blood specimens were obtained by one of us. Salk poliomyelitis vaccine,* procured from the Pharmacy of the University Hospitals, State University of Iowa, was given intramuscularly, either alone or combined just before injection with diphtheria-pertussis-tetanus toxoid. Two regimens of administration of the vaccine were used in the study. The study was started in September, 1958, and concluded in October, 1960.

Group A. Infants of Group A were between 9 and 15 weeks of age (median, 10 weeks; mean, 11 weeks) when the first inoculation of Salk vaccine was given. A second inoculation was given one month later, a third injection 6 or 7 months after the second, and a fourth injection 4 to 6 months after the third.

Blood was obtained from the infants at the time of each inoculation and one month after the second, third, and fourth inocula-

From the Departments of Pediatrics and Microbiology, Bowman Gray School of Medicine, Winston-Salem, N. C., and Department of Pediatrics, State University of Iowa, Iowa City, Iowa.

**Address, The Bowman Gray School of Medicine, Wake Forest College, Winston-Salem 7, N. C.*

*The vaccine was prepared by Eli Lilly and Company (7 lots) and Wyeth Laboratories (2 lots). Since the study was designed to obtain data that would be of practical value to the practicing physician, no attempt was made to obtain vaccine of especially high antigenicity.

Table I. Group A. Poliovirus antibody titers in sera of infants at designated intervals during course of Salk vaccine administration

Blood obtained	*Infants (No.)*	*Median age (weeks)*	*No. 1:256 or greater*	*No. 1:64*	*No. 1:16*	*No. 1:4*	*No. less than 1:4*
Polio I							
Polio inoculation 1	25	10	0	2	8	5	10
Polio inoculation 2	25	14	1	2	4	7	11
Blood only	25	18	0	0	4	8	13
Polio inoculation 3	19	40	0	0	0	4	15
Blood only	12	44	0	2	5	5	0
Polio inoculation 4	10	60	0	0	2	3	5
Blood only	12	64	4	5	1	2	0
Polio II							
Polio inoculation 1	25	10	3	4	6	6	6
Polio inoculation 2	25	14	1	4	8	4	8
Blood only	25	18	0	2	7	9	7
Polio inoculation 3	19	40	0	0	1	5	13
Blood only	12	44	1	1	1	2	7
Polio inoculation 4	10	60	0	1	1	1	7
Blood only	12	64	3	3	5	1	0
Polio III							
Polio inoculation 1	25	40	0	3	6	7	9
Polio inoculation 2	25	10	0	2	7	4	12
Blood only	25	14	1	2	5	8	9
Polio inoculation 3	19	18	0	1	0	2	16
Blood only	12	44	2	3	2	1	4
Polio inoculation 4	10	60	1	0	3	1	5
Blood only	12	64	5	4	3	0	0

Table II. Group B. Poliovirus antibody titers in sera of infants at designated intervals during course of Salk vaccine administration

Blood obtained	*Infants (No.)*	*Median age (weeks)*	*No. 1:256 or greater*	*No. 1:64*	*No. 1:16*	*No. 1:4*	*No. less than 1:4*
Polio I							
Polio inoculation 1	20	6	6	6	1	3	4
Polio inoculation 2	17	10	3	7	0	4	3
Polio inoculation 3	19	14	1	5	8	2	3
Blood only	20	18	3	4	9	2	2
Polio inoculation 4	16	40	1	1	2	3	9
Blood only	13	44	4	1	2	3	3
Polio II							
Polio inoculation 1	20	6	4	7	5	4	0
Polio inoculation 2	17	10	0	6	3	7	1
Polio inoculation 3	19	14	2	4	6	5	2
Blood only	20	18	1	2	8	6	3
Polio inoculation 4	16	40	0	1	2	2	11
Blood only	13	44	2	1	2	5	3
Polio III							
Polio inoculation 1	20	6	3	4	4	2	7
Polio inoculation 2	17	10	0	5	3	6	3
Polio inoculation 3	19	14	0	4	5	4	6
Blood only	20	18	1	3	7	5	4
Polio inoculation 4	16	40	0	0	3	4	9
Blood only	13	44	2	1	3	4	3

tions. Twenty-five of the 30 infants initially enrolled in this group could be followed at least until blood was obtained one month after the second injection. Nineteen were given a third inoculation and 12 of these were available for follow-up studies one month later. All 12 of the infants were subsequently given a fourth inoculation and sera for antibody studies were obtained one month later.

Group B. The infants in Group B were 5 to 7 weeks of age (median, 6 weeks; mean, 5.6 weeks) when the first injection was given. These infants received three inoculations at monthly intervals and a fourth inoculation 6 to 7 months after the third. Twenty infants were initially enrolled in this study and could be followed at least until blood was obtained one month after the third injection. Thirteen infants were studied one month after administration of a fourth injection.

METHODS

Venous blood was allowed to clot at room temperature. Serum was removed and stored at –20° C until ready for serologic testing. Specimens shipped from Iowa City to Winston-Salem were packed in dry ice and were still in the frozen state on arrival in Winston-Salem.

Neutralization tests. All neutralization tests were performed in monkey kidney (rhesus) cell cultures. Mixture 199 with penicillin and streptomycin was used as the maintenance medium for the cell cultures. Approximately 100 $TCID_{50}$'s per 0.1 ml. of each of the three types of polioviruses were used in each test. In every instance control tubes were inoculated with the same amount of virus. The sera were incubated at 56° C. for 30 minutes. They were then diluted from 1:4 to 1:1,024 and equal amounts of each dilution of serum and virus were incubated for one hour at room temperature. A 0.2 ml. aliquot of each mixture of serum and virus was inoculated into 2 or 3 cell cultures and the cultures were observed daily for cytopathic effects. The final reading, made 48 hours after the control cultures first showed cytopathic effect, coincided with greatest cytopathic effect in control cultures. The titer of serum was taken as that dilution of serum which completely prevented cytopathic effects. Stock suspensions of polioviruses used in this study were constantly retitered in order to assure uniformity of virus inoculum.

In all instances, at least 2 sera from the same patient were tested simultaneously. Many of the titers were repeated to insure reproducibility of results.

RESULTS

Group A. Serum obtained from the infants at the time of the first inoculation revealed that 60 per cent had titers of 1:4 or greater against Type I poliovirus, 76 per cent had titers of 1:4 or greater against Type II poliovirus, and 64 per cent had titers of 1:4 or greater against Type III poliovirus (Table I, Fig. 1). Presumably these antibodies were passively transferred from the mother. The titers diminished in spite of 2 inoculations of polio vaccine and by the time that the third injection was to be given at approximately 8 to 10 months of age, only 21 per cent (4 of 19 infants) had detectable titers* of antibodies against Type I poliovirus; 31 per cent (6 of 19 infants) had detectable titers of antibodies against Type II poliovirus; and 16 per cent (3 of 19 infants) had detectable titers of antibodies against Type III poliovirus (Table I; Fig. 1).

Sera obtained one month after the third inoculation showed that all infants had developed detectable titers of antibodies against Type I poliovirus, 5 of 12 infants had detectable titers against Type II poliovirus, and 8 of 12 infants had detectable titers against Type III poliovirus. As may be seen from Fig. 2, only 50 per cent of infants with antibody titers of 1:16 or greater at the time of the first inoculation developed detectable titers one month after the third inoculation. Many of these infants no longer

*The designation, "detectable titer," is used in this presentation to indicate a titer of neutralizing antibodies of 1:4 or greater.

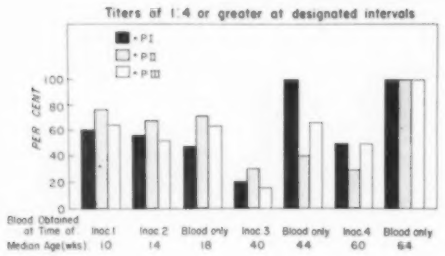


Fig. 1. Group A. Per cent of infants with poliovirus antibody.

had detectable titers of antibodies by the time the fourth inoculation was given (4 to 6 months after the third). At that time only 5, 3, and 5, of 10 infants had detectable titers of antibodies against Types I, II, and III polioviruses, respectively.

One month after the fourth inoculation all infants demonstrated detectable titers of antibodies against Types I, II, and III.

Group B. Sera obtained at the time of the first inoculation contained neutralizing antibodies of 1:4 or greater against Types I, II, and III polioviruses in 80 per cent, 100 per cent, and 65 per cent, respectively, of infants of Group B (Table II, Fig. 3).

At the time of the fourth (booster) inoculation, only 7 of 16 infants had antibody titers of 1:4 or greater against poliovirus Type I, 5 of 16 infants had detectable titers against Type II, and 7 of 16 infants had similar titers against Type III poliovirus. One month after the fourth inoculation 10 of 13 infants had titers of 1:4 or greater against the 3 types of polioviruses. In this group, then, 3 of 13 infants did not have antibodies against Types I, II, and III at the end of the vaccine administration.

There was no indication that combining the vaccine with diphtheria-pertussis-tetanus or giving it separately influenced the final titer in sera of infants of either group.

DISCUSSION

Inability to detect neutralizing antibodies at a dilution of serum of 1:4 is commonly interpreted as evidence of lack of immunity while the presence of neutralizing antibodies

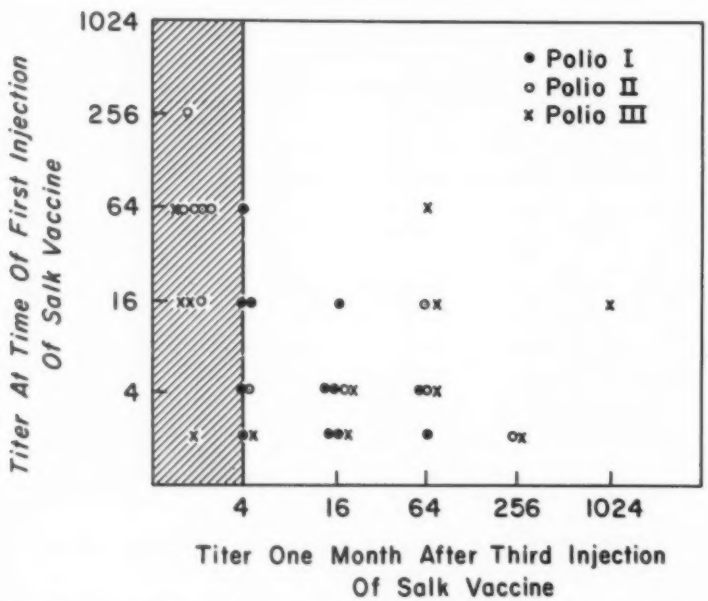


Fig. 2. Group A. Relation between poliovirus antibody titer at time of first Salk injection and one month after third injection.

at such a titer or greater is commonly considered to be evidence of immunity. Although the presence or absence of detectable neutralizing antibodies in the serum is currently the most reliable indication of the presence or absence of immunity to poliomyelitis, it is known that infection may occur in the presence of circulating neutralizing antibodies. Likewise, a child without a detectable titer of neutralizing antibodies may, when confronted with a viral pathogen, escape clinical evidence of disease and exhibit a rapid rise in neutralizing antibodies in response to antigenic stimulation. However, although failure to demonstrate the presence of neutralizing antibodies in titer of 1:4 or greater is not synonymous with lack of immunity, this criterion may provide a useful index of the efficacy of a given regimen of Salk vaccine administration.

Four variables in the present study are (1) age at time of inoculation, (2) number of inoculations during the first few months of life, (3) presence or absence of diphtheria-pertussis-tetanus in the poliomyelitis vaccine, and (4) varying potency of the different lots

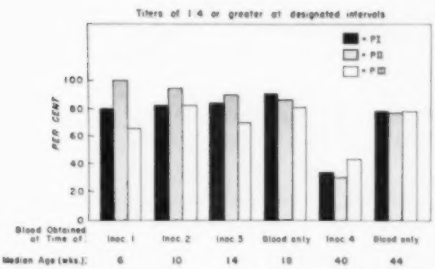


Fig. 3. Group B. Per cent of infants with poliovirus antibody.

of vaccine employed. The third factor did not appear to influence the final results and the importance of the fourth factor cannot be assessed from the present data. All the vaccine used in the study was similar to that commonly employed in practice. No attempt was made to secure vaccine of high antigenicity as this would have limited the usefulness of the data obtained from the study.

The infants of Group A were between 9 and 15 weeks of age when the first inoculation was given and the second inoculation was given one month later. Blood obtained

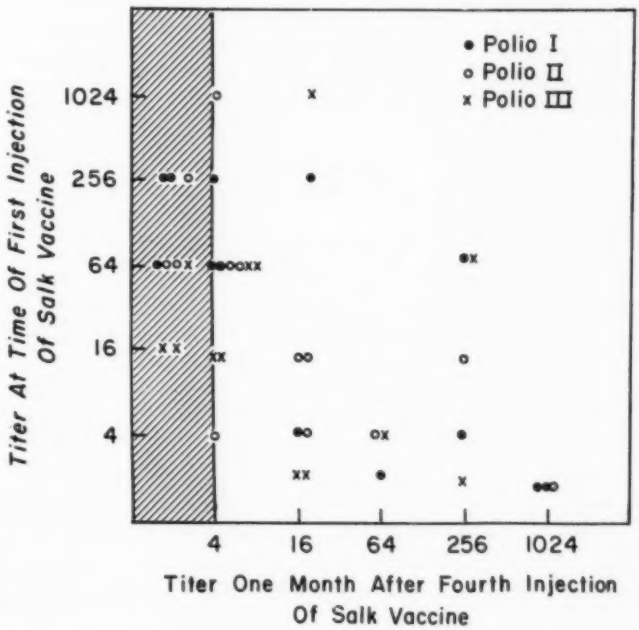


Fig. 4. Group B. Relation between poliovirus antibody titer at time of first Salk injection and one month after fourth injection.

at the time of these inoculations and one month after the second, revealed gradual diminution of titers of antibodies. The third inoculation was given 6 to 7 months after the second when antibody titers were low or not detectable. Blood obtained one month after the third inoculation revealed that all infants responded with development of detectable titers of antibodies against Type I, but 59 per cent and 33 per cent, respectively, did not have detectable titers against Types II and III. For this reason, a fourth polio inoculation was given 5 to 6 months after the third; one month later all infants (median age of infants, 64 weeks) demonstrated detectable titers of antibodies against the three types of polioviruses.

Infants of Group B were between 5 and 7 weeks of age at the time of the first inoculation; they received three inoculations of vaccine at monthly intervals. A fourth inoculation was given 6 to 7 months after the third. At the time the fourth inoculation was given, percentages of the infants of Group B (median age, 40 weeks) who lacked detectable titers of antibodies against the three types of poliovirus were similar to the percentages described for infants of Group A (median age, 60 weeks). However, sera obtained one month after the fourth inoculation revealed that detectable titers of antibodies against poliovirus Types I, II, and III were not demonstrable in sera of 3 of 13 infants of Group B (median age, 44 weeks). This is in contrast to the results previously cited for infants of Group A.

It is unwise to make far-reaching conclusions from data obtained from a relatively small number of infants. However, it would appear that an appreciable number of infants less than 8 weeks of age at the time of administration of the first Salk polio inoculation will not respond satisfactorily after the fourth injection. The data also suggest that passively transferred antibodies interfere with active immunization with Salk vaccine. Thus, an infant with a titer of 1:16 or greater at the time of administration of the first inoculation is likely to respond less than an infant with a lower initial titer.

SUMMARY

Salk poliomyelitis vaccine was administered according to two regimens. The infants in Group A were given the first injection at the age of 10 weeks (median), the second at 14 weeks, the third at 40 weeks, and the fourth at 60 weeks. Infants in Group B received their first injection at 6 weeks (median), the second at 10 weeks, the third at 14 weeks, and the fourth at 40 weeks of age.

All infants of Group A had serum titers of neutralizing antibodies of 1:4 or greater one month after the fourth injection which was given at 57 to 64 weeks of age.

Three of 13 infants of Group B had titers of neutralizing antibodies less than 1:4 against one or more of the three types of poliovirus one month after the fourth inoculation given between 36 and 45 weeks of age.

A titer of passively transferred neutralizing antibodies of 1:16 or greater at the time the first inoculation was given seemed to interfere with response to active immunization.

REFERENCES

1. Gaisford, W., Feldman, G. V., and Perkins, F. T.: Current Immunization Problems, J. PEDIAT. **56:** 319, 1960.
2. Bridges, R. A., Condie, R. M., Zak, S. J., and Good, R. A.: The Morphologic Basis of Antibody Formation, Development During the Neonatal Period, J. Lab. & Clin. Med. **53:** 331, 1959.
3. Osborn, J. J., Dancis, J., and Julia, J. F.: Studies of the Immunology of the Newborn Infant. I. Age and Antibody Production, Pediatrics, **2:** 736, 1952.
4. Dancis, J., Osborn, J. J., and Kunz, H. W.: Studies of the Immunology of the Newborn Infant. IV. Antibody Formation in the Premature Infant, Pediatrics **12:** 151, 1953.
5. Eichenwald, H. F., and Kotsevalov, O.: Immunologic Responses of Premature and Full-Term Infants to Infection With Certain Viruses, Pediatrics **25:** 829, 1960.
6. Koprowski, H., Norton, T. W., Hummeler, K., Stokes, J., Hunt, A. D., Flack, A., and Jervis, G. A.: Immunization of Infants With Living Attenuated Poliomyelitis Virus, J. A. M. A. **162:** 1281, 1956.
7. Spigland, I., and Goldblum, W.: Immunization of Infants With Formalinized Poliomyelitis Vaccine (Salk Type), Pediatrics **25:** 812, 1960.
8. Batson, R., Christie, A., Mazur, B., and Barrick, J. H.: Response of the Young Infant to Poliomyelitis Vaccine Given Separately and Combined With Other Antigens, Pediatrics **21:** 1, 1958.

Sickle cell anemia in the first 2 years of life

Mary Ellen Haggard, M.D.* and Rose G. Schneider, Ph.D.

GALVESTON, TEXAS

SICKLE CELL ANEMIA, a hereditary disorder well known in an adult Negro population, has been infrequently described in the period of early infancy of the American Negro. Although onset of manifestations of the disease within the first or second year of life has been a prominent part of the natural history of the disease in Africa,[1, 2] no cases of clinical sickle cell disease have been described in the immediate postnatal period and, before 1950, only 5 such cases had been identified in the first 3 months of life in the United States. In recent years, 7 additional cases in this age group have been recorded.[4-8]

The relative paucity of sickling erythrocytes in early infancy has been known for sometime[9, 10] and has recently been explained by the fact that S hemoglobin, being an adult type, does not reach maximum production in early life.[11] Even in the newborn infant genetically destined to develop a hemoglobinopathy, the hemoglobin is predominantly of the fetal type; only as fetal hemoglobin is replaced by an adult type (A, S, C, etc.) can hemoglobinopathies develop.

From the Department of Pediatrics, the Hematology Research Laboratory, and the Tissue Metabolism Laboratory of The University of Texas Medical Branch, Galveston, Texas.

Aided by Grant A780 from the United States Public Health Service.

**Address, Department of Pediatrics, University of Texas Medical Branch, Galveston, Texas.*

In a study of 7 infants with sickle cell trait, Schneider and Haggard[11] found that at birth only 3 to 15 per cent of the erythrocytes contained S hemoglobin as indicated by their capacity to sickle; in free electrophoresis the S hemoglobin values in the blood of these infants ranged from not demonstrable to 21 per cent. In successive blood samples the number of sickling erythrocytes and the amount of S hemoglobin rose concomitantly with the fall in F hemoglobin. Only after the age of 4 months, when most of the F hemoglobin had disappeared, did the degree of sickling and the amount of S hemoglobin reach adult proportions.

The present report deals with 54 Negro children homozygous for hemoglobin S, of whom 26 were examined by us and the diagnosis made before the age of 2 years. Among these were 2 siblings studied from birth or shortly after. Among the remaining 28 children, ranging from 25 months to 11 years of age at the time of initial examination and diagnosis, were an additional 14 who actually had symptoms referable to sickle cell anemia before their second birthdays.

METHODS

Sickling preparations were made with sodium metabisulfite.[12] In preparations from young infants the cover slips were sealed with melted paraffin and allowed to stand

for several hours or until complete sickling was obtained in similar control preparations. The percentage of sickling was determined by counting 1,000 to 2,000 cells under 400× magnification. Free and paper electrophoretic analyses were performed by methods previously described.[13] F hemoglobin was determined by the method of alkali denaturation.[14] Reticulocyte and platelet levels were obtained by the indirect method of counting from wet preparations stained with brilliant cresyl blue. Hemoglobin levels were determined from spectrophotometric oxyhemoglobin in some instances and by cyanomethemoglobin methods in others.

Clinical findings. Of the infants studied during the neonatal period, none developed clinical symptoms of sickle cell anemia before the age of 3 months; nor was there any evidence, historically, that any of the infants seen at a later age experienced difficulty in this early period. In the 3 to 6 month age group clinical manifestations were still relatively few, being noted either by history or physical examination in only 9 instances. In this age group, diagnosis of sickle cell anemia was usually made at the time of some intercurrent respiratory infection with a disproportionate amount of fever and irritability, or because of close hematologic observation of an infant with a family history of sickle cell disease. Another 20 children developed symptoms between the sixth and twelfth months, so that, in contrast to previous observations,[15] 29 or over one half the patients had their onset before the end of the first year, and, in 40 or about three fourths symptoms appeared within the first 2 years of life. Twenty-six of these 40 patients were actually examined by us before the age of 2 years (Table I). The liver was often palpable, and enlargement to more than 2 cm. below the right costal margin was encountered in 9 infants. The spleen was palpable in 15 of the 26 infants. Of these 15, 5 were in crisis at the time of the first evaluation. These 5 had the most significant degree of splenic enlargement, 4 to 6 cm. below the left costal margin. This is in agreement with the observations of Trowell[1] who found the spleen palpable in 30 of 37 infants with sickle cell disease.

Table I. Age at onset of symptoms referable to homozygous hemoglobin S disease

Age (months)	*No. of cases*	*% of total*
<3	0	
3 to 6	9	16.7
6 to 12	20	37.0
12 to 18	5	9.3
18 to 24	6	11.1
>24	14	25.9
Total	54	

Trowell has also called attention to a specific type of osteopathy as one of the most noteworthy findings in infancy. Among the 54 patients in this series, osteopathy had occurred in 25 before the end of the second year, so that the so-called symptomatic crisis was comparatively common. Swelling, extreme tenderness, and warmth, usually over the metacarpals or proximal phalanges, and usually accompanied by fever, were the most common signs of bone involvement; the feet and long bones were affected much less frequently. In only one instance did these symptoms of bone involvement occur before the sixth month of life. Often a tentative diagnosis of acute pyogenic osteomyelitis was suggested by the initial examiner, and one case of osteopathy was indeed complicated by a *Salmonella typhimurium* infection.

In those infants with swelling over the hands and feet, radiologic evaluation 2 to 3 weeks following the onset of symptoms often revealed periosteal reactions with rarefaction of the medulla. This reaction was observed most frequently in the metacarpals, although the proximal phalanges and metatarsals were also often involved. The striking destruction of the long bones observed in 2 of the children in this series has been described elsewhere.[16]

Hematologic findings. After the sixth month of life anemia was a consistent finding in these infants and, except at times of crisis, the hemoglobin ranged between 7 and 9 Gm. per cent. The character of the

Table II. Thrombocytopenia in infants with sickle cell anemia

Patient	*Age (months)*	*Hemoglobin (Gm. %)*	*Platelets (per mm.³)*	*Bilirubin (mg. %)*	*Splenomegaly*
R. P. M.	6½	2.8	59,000	2.8	++++
E. F.	7	4.0	77,000	3.4	++++
M. W.	10	3.8	81,000	2.3	++++
J. L. D.	13	3.4	19,000	3.0	++++

anemia is well documented and need not be emphasized here. It may be noted, however, that in the very young infant routine sickling preparations may be erroneously interpreted as negative because only a small number of erythrocytes are capable of sickling. Two of the infants studied because of anemia, on routine examination, had been reported as negative for sickling. In hemoglobin electrophoresis the characteristic SS pattern was ultimately found in all cases, although in samples obtained at a very early age this pattern was obscured by the presence of large amounts of F hemoglobin.

Thrombocytopenia was present in 4 of the infants with pronounced splenomegaly (Table II). Data on one of these are presented below (Fig. 1).

CASE 1

J. L. D., a 13-month-old Negro male, was referred to the clinic because of a mass in the left upper quadrant, first noted at 9 months of age on a routine well-child examination. One week prior to his admission he developed coryza, fever, and irritability, followed by yellow discoloration of the sclerae and dark urine.

Family history. The mother was known to have sickle cell trait. Later a second child was found to have sickle cell anemia.

Physical examination. Observation on admission revealed an afebrile Negro boy with height and weight measurements in the third percentile for his age. He had pale palms and soles and icteric sclerae. The abdomen was protuberant and the spleen extended well below the iliac crest. The liver border was palpated 3 cm. below the right costal margin.

Laboratory data. The findings showed hemoglobin, 3.3 Gm. per cent; erythrocytes, 1.16 million per cubic millimeter; reticulocytes, 21 per cent; leukocytes, 16,600 per cubic millimeter; polymorphonuclear leukocytes, 22 per cent; stab forms, 8 per cent; metamyelocytes, 6 per cent; lymphocytes, 52 per cent; monocytes, 11 per cent; normoblasts, 250 per 100 white blood cells; and sickling positive. In paper electrophoresis, the hemoglobin appeared to be almost entirely of Type S with perhaps a small amount of F. By the method of alkali denaturation, the F hemoglobin value was 8 per cent. The total serum bilirubin was 1.9 mg. per cent, initially, and the indirect was 1.6 mg. per cent. Four days later these values were 3.0 and 1.9 mg., respectively. When it was noted that bleeding following venipunctures was slowly controlled, a platelet count was obtained and found to be 19,000 per cubic millimeter. Bone marrow biopsy did not show the expected increase in erythroid elements, but did reveal an increase in megakaryocytes.

Hospital course. Initial therapy consisted of transfusion with packed red blood cells.

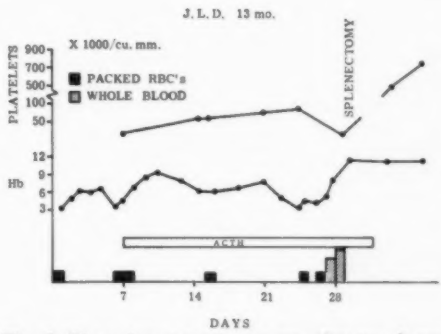


Fig. 1. Thrombocytopenia unresponsive to adrenocorticotropic hormone but responding to splenectomy in an infant with homozygous hemoglobin S disease.

After diagnosis of the thrombocytopenia, adrenocorticotropic hormone was also administered. The platelet count, however, remained well below 100,000. After repeated blood transfusions, the spleen, which weighed 372 grams, and a small accessory spleen were operatively removed. Microscopically, the spleen showed marked congestion; all of the sinuses were extremely engorged and dilated, and there were foci of hemorrhage about the follicles and in the parenchyma. Foci of hemopoietic activity and megakaryocytes were also observed.

The postoperative course was uncomplicated. No further transfusions were required, and the ACTH was gradually discontinued. The hemoglobin level remained about 10 Gm. per cent until the patient was discharged 6 weeks later, and the platelet count rose to 500,000 by the fifth postoperative day. The reticulocyte level declined to 5.8 per cent. Two years later the mother reported that the child had required no further hospitalization, and that serious infection or other illness had not occurred.

RELATION OF SYMPTOMS TO THE QUANTITATIVE DEVELOPMENT OF S HEMOGLOBIN

In Table III are presented serial observations on 2 siblings who were studied from birth or shortly thereafter because their older sister was known to have sickle cell anemia and their parents to be carriers of the sickling trait. Scanning diagrams of successive hemoglobin samples of one of of these infants, J. W., are presented in Fig. 2. In the cord blood 10 per cent of the erythrocytes sickled and the F hemoglobin value was 88 per cent, whereas S hemoglobin by the method of free electrophoresis was about 13 per cent. In the first few successive blood samples the percentage of sickling rose sharply and became maximum at about 4 months. There was also a rapid fall in F hemoglobin with a reciprocal rise in S hemoglobin, but the rate of change became relatively slow after the third month. Indeed, J. W.'s F hemoglobin level remained above 30 per cent until he was well into his second year.

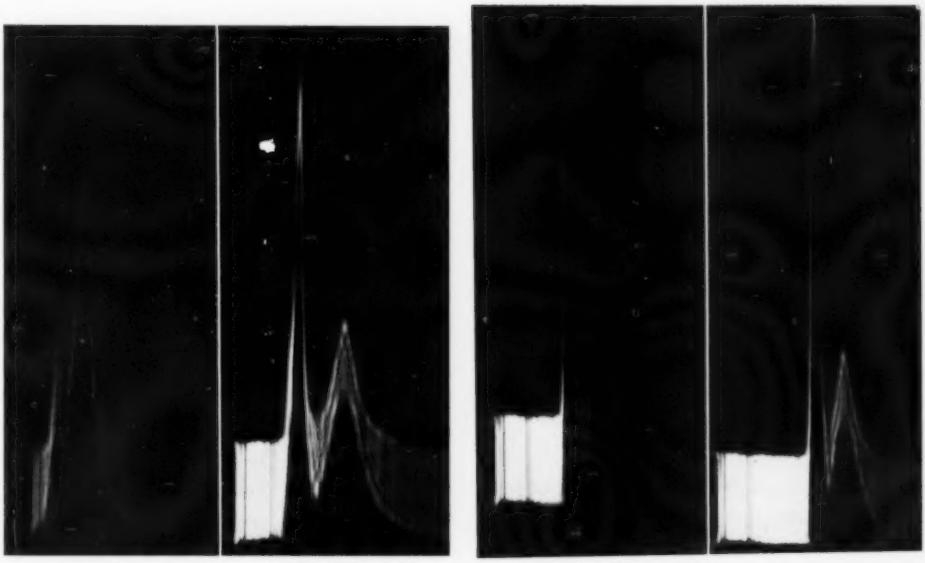
J. W.'s sister, S. W., was first examined at the age of 6 weeks, when 25 per cent of the erythrocytes sickled and the F hemoglobin value was 66 per cent. By paper electrophoresis, most of the hemoglobin appeared to be of the F type, with a small amount of Type S, and an apparent complete absence of hemoglobin A. S. W.'s symptoms, which appeared at 3 months, when 85 per cent of the erythrocytes sickled and the F hemoglobin value was 38 per cent, developed much earlier than her brother's. Indeed, J. W. did not demonstrate symptoms until the age of 22 months, at which time his F hemoglobin value had dropped to 10 per cent. The data do not indicate whether this sharp fall in F hemoglobin preceded or followed the onset of symptoms. By 23 months of age, F hemo-

Table III. Serial observations on siblings with sickle cell anemia

Age (months)	*Hemoglobin*		*Reticulocytes %*		*Serum bilirubin*		*% F hemoglobin*		*% S cells and S hemoglobin**		*Symptoms*	
	J. W.	*S. W.*	*J. W.*	*S. W.*	*J. W.*	*S. W.*	*J. W.*	*S. W.*	*J. W.*	*S. W.*	*J. W.*	*S. W.*
Newborn	21						88		10 (13)*		--	-
1½								66		25		-
3	9.8	6.2	1.8	7		0.8		38	56 (50)	85†	-	+
4							44	33	90†(50)		-	++
6	8	6.4		5.6			38	23	(64)		-	+++
8	10	9	5.6		2		37		(70)		-	-
13	10	8.3	13				32				-	
22	7.8		6.4				10				++	
23	5.7	7.7		17.2	2.2		15	12		100	+++	-

*Figures in parentheses refer to S hemoglobin values as determined by scanning diagrams.

†After the age of 4 months virtually all the erythrocytes sickled.



Cord blood 3 months 4½ months 6 months

Fig. 2. Scanning diagrams of successive samples of hemoglobin of J. W. Ascending patterns from right to left of 1 per cent carbonmonoxyhemoglobin in cacodylate buffer, pH 6.5, μ0.1. (In each diagram the leading peak represents the S hemoglobin and the slower one the F hemoglobin.)

globin levels were very similar in both siblings; at this age J. W.'s clinical symptoms appeared more severe than his sister's.

DISCUSSION

In very early infancy clinical and hematologic indications of the homozygous S state may be completely lacking. Only a relatively small percentage of the erythrocytes are capable of sickling and in electrophoresis the hemoglobin is predominantly of the fetal type, with only a small amount of the adult hemoglobin S being present. After about 4 months of age practically all of the erythrocytes sickle, although the percentage of F hemoglobin may remain high for many months, indeed, well into adult life.[14] At any rate, there appears to be no predictable correlation between the F hemoglobin levels and the onset or severity of symptoms. In patient J. W. the onset of symptoms coincided with a sharp fall in F hemoglobin, but the precise relationship between these two events is not clear.

The increased severity of the hemolytic state associated with splenomegaly in sickle cell anemia has been repeatedly emphasized and is well documented by Sprague and Paterson,[17] but the thrombocytopenia which may accompany massive splenomegaly in sickle cell anemia has received little attention, although it has been frequently described in association with massive splenomegaly in other conditions. Singer[18] has made brief mention of adults with sickle cell anemia who developed splenic vein thrombosis, followed by massive splenomegaly and thrombocytopenia with bleeding into the spleen. Among the 4 infants with thrombocytopenia in the present study, only one showed clinical evidence of an increased tendency to bleed. It is noteworthy that all 4 of these infants were in crisis at the time of study, as indicated by the degree of anemia (Table II), and that all had massive splenomegaly. The role of the spleen in the development of thrombocytopenia in these infants is a matter of speculation. The return to a normal platelet count with subsidence of the crisis and a decrease in the

size of the spleen in one instance suggests the possibility of mechanical factors, with the spleen acting as a reservoir for platelets as it may for erythrocytes. However, microscopic study of the spleen in the infant who underwent splenectomy failed to reveal an increased number of platelets. Another possibility is that the same factor responsible for precipitation of a crisis, e.g., infection, may have precipitated the development of thrombocytopenia. In any event determination of platelet levels during sickle cell crisis in any infant with splenomegaly would seem indicated.

SUMMARY

Studies are presented on 54 Negro children with sickle cell anemia, of whom 26 were examined and the diagnosis found before the age of 2 years. In 2 siblings, one studied from birth and the other from the age of 6 weeks, there was no strict correlation between the rise in S hemoglobin, the reciprocal fall in F hemoglobin, and the development of symptoms. Clinical manifestations did not appear in any of the 54 children before 3 months of age. Symptoms were noted, however, either by personal observation or by history in about one half of the patients before the age of 1 year and in three fourths of the patients before 2 years of age. Particularly noteworthy findings were the osteopathy involving, primarily, the metacarpals and proximal phalanges, and the splenomegaly, which in 4 instances was associated with thrombocytopenia.

REFERENCES

1. Trowell, H. C., Raper, A. B., and Welborn, H. F.: The Natural History of Homozygous Sickle Cell Anemia in Central Africa, Quart. J. Med. **26:** 401, 1957.
2. Lambotte-Legrand, J., and Lambotte-Legrand, C.: L'Anémie à hématies falciformes en Afrique Noire, Sang **23:** 560, 1952.
3. Wollstein, M., and Kneidel, K. V.: Sickle Cell Anemia, Am. J. Dis. Child. **36:** 998, 1928.
4. Cohen, S. M., Miller, B. M., and Orris, H. W.: Fatal Sickle Cell Anemia in a One-Month-Old Infant, J. PEDIAT. **30:** 468, 1947.
5. Frazier, C. A., and Rice, C. E.: Neonatal Sickle Cell Anemia, J. A. M. A. **143:** 1065, 1950.
6. Leikin, S. L., and McCoo, J. W.: Sickle Cell Anemia in Infancy, A. M. A. J. Dis. Child. **96:** 51, 1958.
7. Erlandson, M. E., and Hilgartner, M.D.: Hemolytic Disease in the Neonatal Period and Early Infancy, J. PEDIAT. **54:** 566, 1959.
8. Jenkins, M. E., Scott, R. B., and Baird, R. L.: Studies in Sickle Cell Anemia. XVI. Sudden Death During Sickle Cell Anemia Crises in Young Children, J. PEDIAT. **56:** 30, 1960.
9. Watson, J.: The Significance of the Paucity of Sickle Cells in Newborn Negro Infants, Am. J. M. Sc. **215:** 419, 1948.
10. Scott, R. B., Crawford, R. P., and Jenkins, M.: The Incidence of Sicklemia in the Newborn Negro Infant, Am. J. Dis. Child. **75:** 842, 1948.
11. Schneider, R. G., and Haggard, M. E.: Sickling, A Quantitatively Delayed Genetic Character, Proc. Soc. Exper. Biol. & Med. **89:** 196, 1955.
12. Daland, G. A., and Castle, W. R.: A Simple and Rapid Method for Demonstrating Sickling of Red Blood Cells; the Use of Reducing Agents, J. Lab. & Clin. Med. **33:** 1082, 1948.
13. Schneider, R.: Incidence of Hemoglobin C Trait in 505 Normal Negroes: A Family With Homozygous Hemoglobin C and Sickle-Cell Trait Union, J. Lab. & Clin. Med. **44:** 133, 1954.
14. Singer, K., Chernoff, A. I., and Singer, L.: Studies on Abnormal Hemoglobins. II. Their Identification by Means of the Method of Fractional Denaturation, Blood **6:** 429, 1951.
15. Wintrobe, M. M.: Clinical Hematology, Philadelphia, 1956, Lea & Febiger, chap. 13, p. 680.
16. Rowe, C., and Haggard, M. E.: Bone Infarcts in Sickle Cell Anemia, Radiology **68:** 661, 1957.
17. Sprague, C. C., and Paterson, J. C. S.: Role of the Spleen and Effect of Splenectomy in Sickle Cell Disease, Blood **13:** 569, 1958.
18. Singer, K.: Hereditary Hemolytic Disorders Associated With Abnormal Hemoglobins, Am. J. Med. **18:** 633, 1955.

What is arrested hydrocephalus?

Robert W. Schick, M.D., and Donald D. Matson, M.D.*

BOSTON, MASS.

WHEN operative procedures are developed which demonstrably alter favorably the course of a disease, then it becomes of paramount importance to define the indications and limitations of such technical maneuvers as promptly and as accurately as possible. With the steadily increasing use of various operations which divert cerebrospinal fluid in the treatment of hydrocephalus,[1-10] renewed interest has understandably become manifest among pediatricians and general physicians, as well as among neurosurgeons, in the desirability and effectiveness of such treatment.

There is little purpose in carrying out technical exercises which reduce intracranial pressure in infants who have already suffered irreversible brain damage to a degree which obviates useful survival. This conclusion seems to be generally recognized, even if not universally followed. It is not always as easy, however, to define indications for surgical treatment of early or mild hydrocephalus, or to evaluate the results of treatment in such patients. Discussion of the latter problem is the purpose of this brief report.

Hydrocephalus implies enlargement of the intracranial spaces which contain cerebrospinal fluid because this fluid is, or at some time has been under increased pressure. Hydrocephalus becomes asymptomatic and clinically unimportant when this pressure has been reduced to normal levels either by a surgical operation or by spontaneous arrest.

In the adult or older child with functionally closed cranial sutures, the clinical sequelae of hydrocephalus are often acute and usually produce a reasonably standard array of symptoms and signs. In the young infant with ununited sutures, however, the clinical findings may be much more subtle, or indeed, entirely absent. This may make accurate evaluation of the adequacy of cerebrospinal fluid circulation and absorption difficult unless the growth of such an infant is followed with extreme care.

There is little written about what constitutes "arrested" hydrocephalus in early childhood and the relative prognostic significance of this state as compared with mildly progressive hydrocephalus. Hydrocephalus has been variously estimated to become arrested spontaneously in 10 to 50 per cent of patients.[11, 12] The meaning of such statistics is difficult to determine since hydrocephalus is not a disease in itself, but a pathologic condition due to a great variety of causes.

It seems important, however, to attempt to define as precisely as possible what is meant by "arrested" hydrocephalus. Several alternatives are possible as far as head growth is concerned following surgical or so-called

From the Department of Neurosurgery, The Children's Hospital Medical Center, Boston, Mass.

**Address, The Children's Hospital Medical Center, 300 Longwood Ave., Boston 15, Mass.*

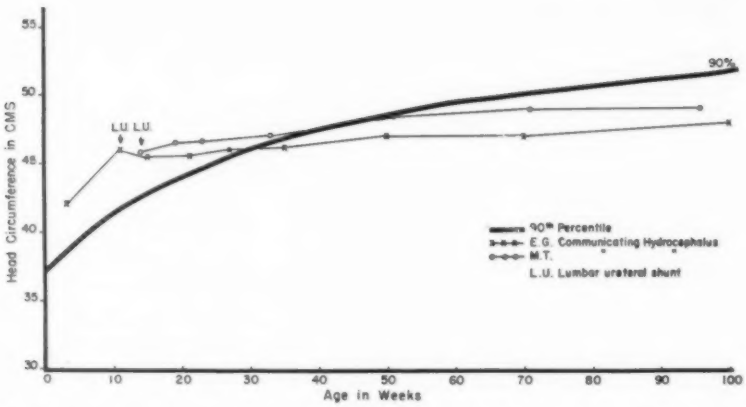


Fig. 1. Head growth in 2 patients following successful lumbar-ureteral shunts for communicating hydrocephalus.

"spontaneous arrest" of hydrocephalus. First, further head growth may cease altogether until growth of the child catches up to the size of the head, that is, until both head and body growth are again in normal relationship; after this, head growth is resumed at a normal rate. Second, the head may actually become smaller following spontaneous or surgical arrest, with delayed resumption of growth at a normal rate when the body catches up. Third, the rate of growth may decrease but continue steadily so that it parallels the normal growth curve but still remains above it. It is our contention that it is not justifiable to consider hydrocephalus arrested and optimum treatment achieved in the latter circumstances. In a young infant, an already enlarged head should not continue to grow at all until the body size has caught up to the head size and each then proceeds within its normal range.

During the past several years, a group of

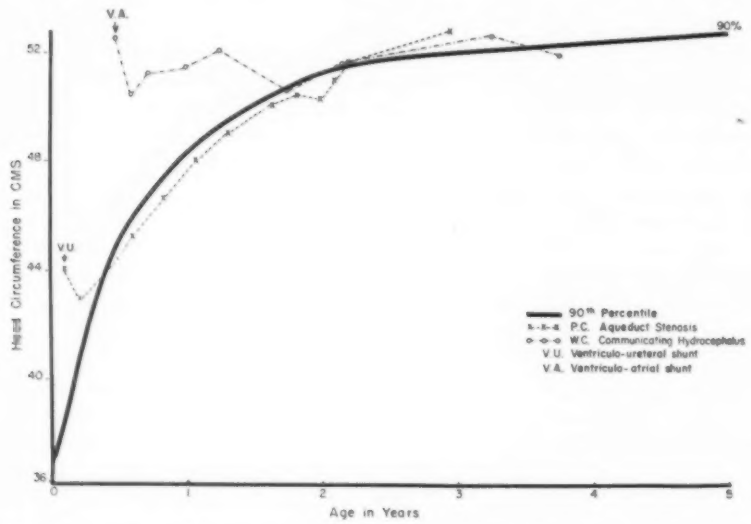


Fig. 2. Three year follow-up of head growth in patients after successful ventriculo-ureteral and ventriculoatrial shunts for noncommunicating and communicating hydrocephalus.

patients have been followed by the neurosurgical service of the Children's Hospital Medical Center, Boston, who have prompted the present attempt at a more precise definition of "arrested" hydrocephalus. In order to clarify what actually happens to the size of an infant's head when hydrocephalus has been arrested, we first studied the head growth pattern of patients with hydrocephalus who have had one or more of the several shunting procedures currently in use. Forty such patients, all with definite hydrocephalus treated by a shunting operation, were investigated; none of this group had an associated myelomeningocele. These patients may be considered as having surgically produced arrest of hydrocephalus. The rate of head growth of these patients has been plotted on an extended normal ninetieth percentile curve with the measurements of Vickers and Stuart.[13] Two growth charts were employed: one showing the first 100 weeks of life was used for infants, and the other, the first 10 years of life, was used for older children.

Typical growth curves from this group of patients are illustrated in Figs. 1, 2, and 3. These demonstrate that following a successful shunting procedure in infancy the head circumference (occipitobregmatic) will generally decrease from 1 to 2 cm. The younger the infant, and the greater the size of the head above normal for that age, the greater will be the decrease in the weeks after operation. If the shunt remains patent, head growth then ceases or occurs at a very slow rate so that the head circumference remains the same or remains below the ninetieth percentile curve.

These curves are all remarkable in their similarity when a single successful shunting operation has been carried out. In all of these patients, there has been little or no further head growth until sufficient time has elapsed so that the head size again falls into place on the normal ninetieth percentile growth curve. In fact, an earlier resumption of head growth is excellent evidence, and may be the only clue, that a shunt is not functioning; that is, that hydrocephalus is, indeed, not arrested. Since there may or may not be other signs of increased intracranial pressure, it is imperative that regular head measurements be charted.

The next group of patients from this study are illustrated in more detail. The charac-

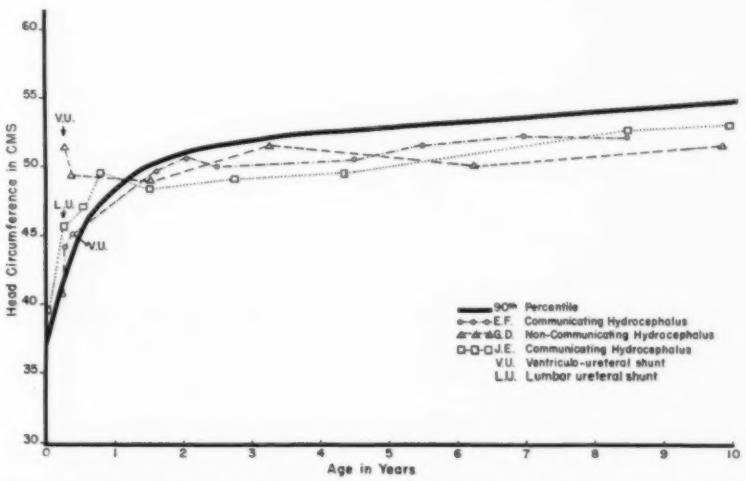


Fig. 3. Prolonged follow-up of head growth in 3 patients after successful lumbar-ureteral and ventriculoureteral shunts for communicating and noncommunicating hydrocephalus.

teristic feature of these patients is slight enlargement of the head but freedom from symptoms of increased intracranial pressure, so that, when they were first seen, they were thought to have "arrested" hydrocephalus. However, regular serial head measurements indicated that they had, instead, a progressive mild hydrocephalus; in other words, a head which was already too large and continuing to grow. Serial measurements in 8 of 20 such patients have indicated continued slow head growth unequivocally and in these shunts have been performed. The remaining patients are still being followed to determine whether or not their hydrocephalus has or has not been arrested. Illustrative case reports follow.

Case 1. S. B., was first seen at 33 weeks of age, having been followed carefully by the family physician as having suspected hydrocephalus because of an abnormal rate of head growth in early infancy (Fig. 4). Examination at this time was remarkable for a head circumference 1.5 cm. above the ninetieth percentile, a slightly cracked-pot percussion note, but approximately normal motor development. Skull roentgenograms revealed prominent sutures but no separation. Bubble ventriculogram demonstrated a communicating type of hydrocephalus with moderately dilated ventricles (Fig. 5). The ventricular and lumbar pressures at this time were 170 mm. of cerebrospinal fluid. He was thought to have mild hydrocephalus and spontaneous arrest. At 62 weeks of age, the head circumference had increased 4 cm., even though a repeat bubble study at that time revealed only slight increase in ventricular dilatation (Fig. 5). A lumbar-ureteral shunt was established at that time and was followed by a 1 cm. decrease in head size.

Case 2. M. F. was first seen at 30 weeks of age because of a respiratory problem. Neurosurgical consultation was sought because of obvious macrocephaly. Examination was remarkable for a head circumference 2.25 cm. above the ninetieth percentile, a slightly abnormal percussion note, and the intermittent downward displacement of the eyeballs. Ventricular and lumbar pressure measurements were normal. Bubble ventriculogram revealed a mildly dilated ventricular system. It was elected to follow the patient with serial head measurements and for a time head growth appeared to parallel the ninetieth percentile (Fig. 6). However, when an actual acceleration of head growth was demonstrated, a lumbar-ureteral shunt was carried out at 43 weeks of age. This was followed by a 0.75 cm. decrease in head size.

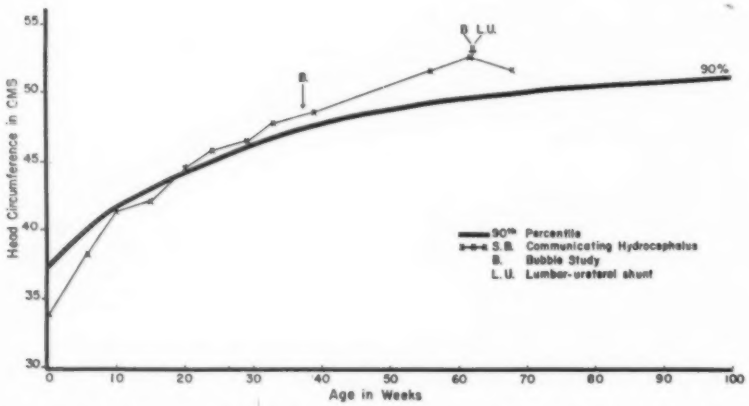
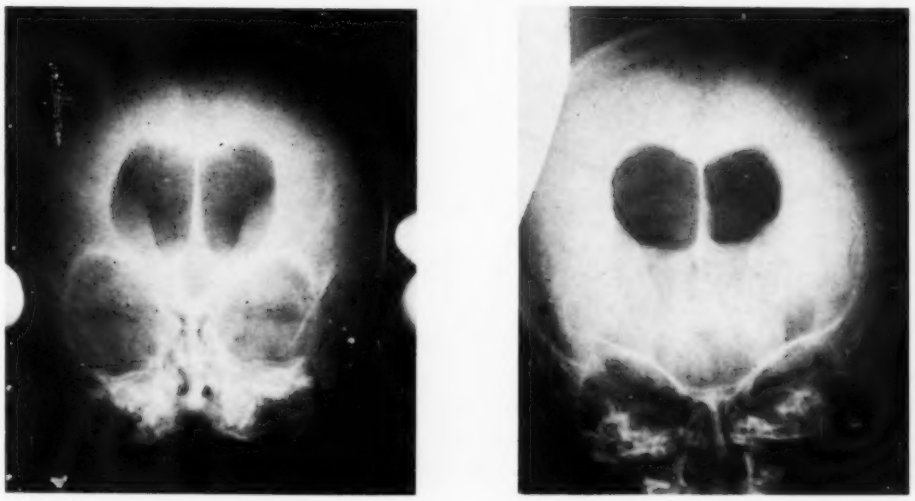


Fig. 4. Case 1. Progressive acceleration of head growth in a child thought to have "arrested" hydrocephalus. Subsequent decrease in head circumference following a lumbar-ureteral shunt.



A *B*

Fig. 5. Case 1. Bubble ventriculogram *(A)* at 35 weeks of age and *(B)* at 62 weeks of age. There has been a slight increase in ventricular dilation in the interim.

Case 3. D. W. was first referred to the Children's Hospital at 11 months of age because of a respiratory tract infection and head enlargement (Fig. 7). Examination revealed obvious macrocephaly but without clinical signs of increased intracranial pressure. He was thought to trail his fraternal twin by 2 to 3 months in motor development. Skull roentgenograms revealed prominent sutures with perhaps slightly elongated interdigitations. Ventricular pressure was 68 to 80 mm. of cerebrospinal fluid and bubble ventriculogram showed communicating hydrocephalus with moderately dilated ventricles. His hydrocephalus was thought to have become arrested. Serial head measurements, however, demonstrated a slight acceleration in the rate of head

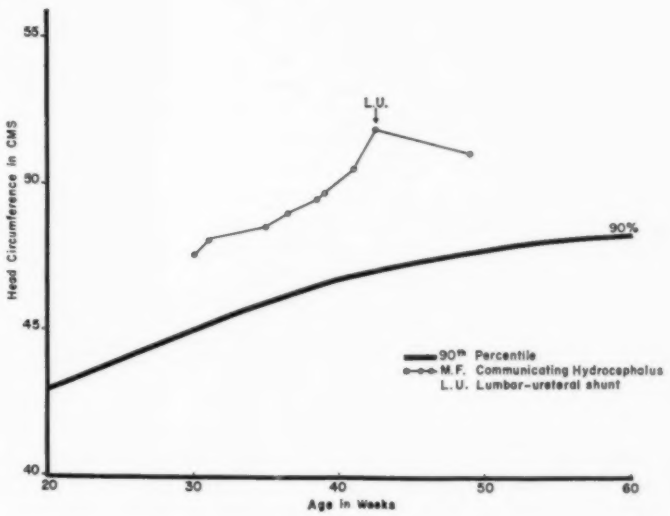


Fig. 6. Case 2. Accelerated head growth in a child thought to have "arrested" hydrocephalus. Decrease in the head circumference following successful lumbar-ureteral shunt.

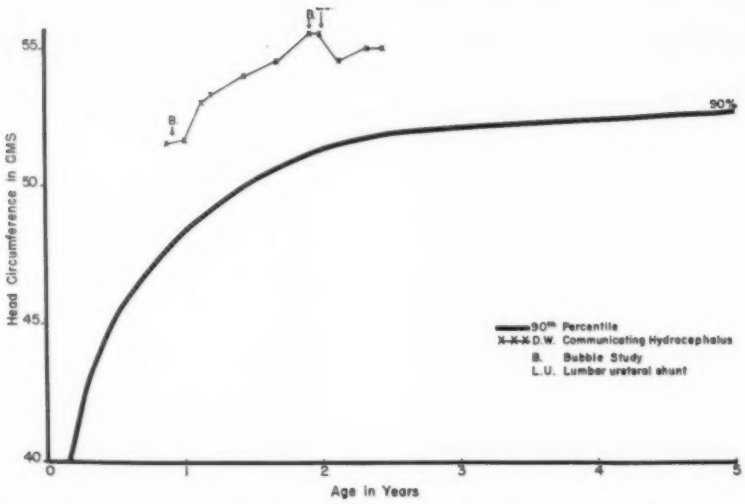


Fig. 7. Case 3. Continued head growth well above the ninetieth percentile curve in a child thought to have "arrested" hydrocephalus. Decrease in head size following a successful lumbar-ureteral shunt.

growth. During this interval he acquired some additional motor skills but at 23 months of age was still not walking independently. A repeat bubble ventriculogram now demonstrated a very slight increase in ventricular size and evidence of an arachnoid block in the basal cisterns (Fig. 8). A 1 cm. decrease in head size was observed following lumbar ureteral shunt.

Case 4. B. A. was first seen at 3½ years of age for evaluation of possible hydrocephalus. She had no symptoms of elevated intracranial pressure and her physical examination was remarkable for a head circumference 5 cm. above the ninetieth percentile growth curve, a slightly abnormal percussion note, but approximately normal motor and mental development for her age. Lumbar puncture pressure was 190 mm. of cerebrospinal fluid and subdural taps were negative. Skull roentgenograms revealed very prominent sutures with elongated interdigitations. Bubble ventriculogram was not performed for fear of possibly upsetting what was thought to be an "arrested" hydrocephalus. There was no head growth for 6 months and it was felt that her hydrocephalus was really arrested (Fig. 9). During the next year, however, there was resumption of head growth at an accelerated rate. Her mental development at the end of this time was still thought to be approximately normal for her age. Skull roentgenograms now revealed obvious separation of the sutures. A ventriculoatrial shunt was

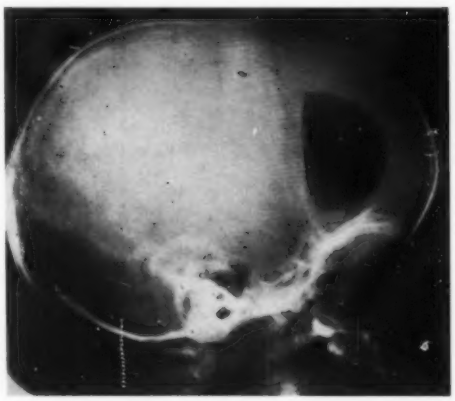


Fig. 8. Case 3. Twelve-hour delayed film during second bubble ventriculogram. Film made in the brow-up position demonstrates moderate hydrocephalus and a block in the basal cistern so that no air gets into the surface subarachnoid pathways.

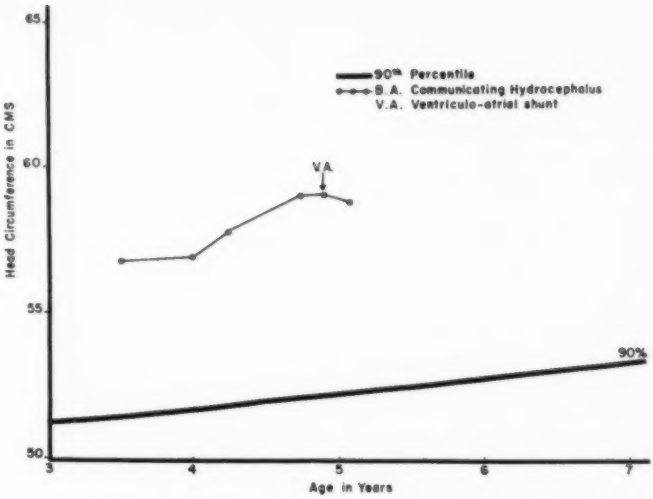


Fig. 9. Case 4. Accelerated head growth in a child thought to have "arrested" hydrocephalus. Slight decrease in head circumference following a successful ventriculoatrial shunt.

established and has been followed by a 0.5 cm. decrease in the head circumference.

These 4 cases are illustrative of slowly progressive hydrocephalus which may be mistaken readily for "arrested" hydrocephalus. All the patients in this group had mild or moderate macrocephaly but few if any clinical or roentgenologic signs of increased intracranial pressure. They all appeared *during this period* to be developing at a normal or only slightly retarded rate. They all had normal lumbar and/or ventricular pressure measurements. Thus, the normal intracranial pressure tended to obscure the presence of progressive hydrocephalus. It is evident, therefore, that in a setting of normal intracranial pressure only serial head measurements will determine whether or not hydrocephalus has been arrested.

Perhaps of even greater importance is the false security that is drawn from the fact that these children continued to acquire motor and mental skills during the periods of observation although, in several cases, at a retarded rate. In 2, an enlarged head was not the primary complaint but was incidentally discovered. This tends also to foster a false sense of security and to delay the diagnosis of active hydrocephalus.

DISCUSSION

It is important to diagnose and treat hydrocephalus as early as possible in order to minimize brain damage. The disastrous results of acute untreated extreme hydrocephalus are only too readily evident. However, the sequelae of chronic, mildly increased intracranial pressure during early life may not be seen for several years. So often a child with mild hydrocephalus masquerading as "arrested" hydrocephalus may appear to be normal up to 4 or 5 years of age, only to show retardation as school problems are encountered. Such children do well when memory and general information are required, but they are not able to integrate knowledge, to exercise initiative, and to use effectively what they have memorized. Progress stops with discouraging frequency at a subnormal intellectual level. As chronologic age increases, the discrepancy between actual mental ability and what it should be for the age becomes greater and greater.

It is our feeling that true spontaneous "arrest" of hydrocephalus, in the terms we have outlined in this paper, probably does not occur in infancy as frequently as has been generally believed. Indeed, it is probable that if hydrocephalus due to the Arnold-Chiari malformation associated with myelomeningocele is excluded, complete spontaneous "arrest" of hydrocephalus in infants under the age of 2 years is extremely rare. It seems probable, therefore, that it may be in mild and slowly progressive hydrocephalus that shunting procedures should yield the most effective, though not necessarily the most immediately dramatic, results.

Considerable concern has followed a report by Laurence,[12] in which he concludes that surgical treatment of hydrocephalus should not be attempted because of the high percentage of spontaneous arrest among patients who survive the first 3 months of life. This conclusion is felt to be a highly dangerous and unjustifiable one. It seems to us, on the contrary, that surgical procedures carried out on patients with extreme degrees of hydrocephalus during the first 3 months of life are not often going to be rewarding because brain damage is already great and the result, even if life is preserved, is not desirable. However, the less severe, but definitely slowly progressive, hydrocephalus of early life should permit of developmental adequacy in direct proportion to the promptness with which true "arrest" is brought about.

Laurence[12] states that in most of the children in his series, "arrest" took place between the ages of 9 months and 2 years. He does not state very accurately his criteria for "arrest," however. As already stressed above, unless serial head measurements are made, and it can be shown that a head which is too large, that is, above the ninetieth percentile figures taken from standard growth curves, does not grow at all until the child catches up to his normal place on the curve, the hydrocephalus cannot in fact be said to have become arrested. As stated, we seriously doubt that hydrocephalus (not associated with myelomeningocele) ever completely ceases spontaneously before the age of 2 years. Although the relative efficiency of cerebrospinal fluid circulation and absorption may be improving during this period, as evidenced by a slowing down of an accelerated rate of head growth, it is not normal unless a head which is already too large ceases to grow at all.

Laurence states that "arrest," or at least nonoperative treatment of hydrocephalus in his patients surviving beyond 3 months of age was compatible with an I.Q. average of 69.7, and that in a certain number a level of greater than 85 was attained. This can hardly be called a satisfactory goal. He does not state how many, if any, of his patients achieved really satisfactory I.Q.'s, that is, more than 100.

If indeed it is true (as Laurence states, but we would doubt) that 47 per cent of hydrocephalic patients undergo spontaneous arrest, mostly by 2 or 3 years of age, then it would seem to be particularly important not to miss this group of patients, but to discover them earlier and attempt to carry out surgical arrest at as young an age as possible so that subsequent cerebral growth can proceed at a normal rate. Only under these circumstances can the final results such as those he quotes, not of survival, not of educability, but of *normal intelligence,* be improved. We are willing to accept added surgical risks and carry out earlier definitive treatment if the percentage of normal children rather than the percentage of survivals can be increased.

How long a child with slowly progressive hydrocephalus should be followed before surgical treatment is recommended at present remains a matter of clinical judgment. Indefinite procrastination, however, simply because there are no symptoms in infancy of increased intracranial pressure, is to be condemned. While the result of treating slowly progressive hydrocephalus after the age of 2 years may often still be beneficial, it must be accepted that the results cannot be as good as if the brain had been able to grow normally prior to this age.

SUMMARY

Complete spontaneous "arrest" of hydrocephalus occurs only rarely in infancy. Hydrocephalus in an infant has not become arrested unless head growth ceases or unless additional head growth proceeds not only at a normal rate but also within or close to a normal circumference range. If our aim is not simply to prolong life but to permit optimal brain growth and maturation wherever possible, mild degrees of progressive hydrocephalus must be treated definitively and as early as possible.

REFERENCES

1. Torkildsen, A.: Ventriculocisternostomy, A Palliative Operation in Different Types of Noncommunicating Hydrocephalus. Oslo, 1947, Johan Grundt Tanum Farlag.
2. Matson, D. D.: A New Operation for the Treatment of Communicating Hydrocephalus. Report of a Case Secondary to Generalized Meningitis, J. Neurosurg. **6:** 238, 1949.
3. Nosik, W. A.: Treatment of Hydrocephalus by Ventriculo-mastoidostomy, J. PEDIAT. **37:** 190, 1950.
4. Matson, D. D.: Ventriculo-ureterostomy, J. Neurosurg. **8:** 393, 1951.
5. Nulsen, F. E., and Spitz, E. B.: Treatment of Hydrocephalus by Direct Shunt From Ventricle to Jugular Vein, S. Forum **2:** 399, 1952.
6. Ransohoff, J., and Hiatt, R.: Ventriculoperitoneal Anastomosis in the Treatment of Hydrocephalus: Utilization of the Supra Hepatic Space: A Preliminary Report, Tr. Am. Neurol. A. **77:** 147, 1952.
7. Harsh, G. R., III: Peritoneal Shunt for Hydrocephalus Utilizing the Fimbria of the Fallopian Tube for Entrance to the Peritoneal Cavity, J. Neurosurg. **12:** 165, 1955.
8. Jackson, I. J., and Snodgrass, W.: Peritoneal Shunts in the Treatment of Hydrocephalus, 4 Year Study of 62 Patients, J. Neurosurg. **12:** 216, 1955.
9. Pudenz, R. H.: Experimental and Clinical Observations on the Shunting of Cerebrospinal Fluid Into the Circulatory System, Proc. Congr. Neurol. Surgeons **5:** 98, 1958.
10. Anderson, F. M.: Ventriculoauriculostomy in Treatment of Hydrocephalus, J. Neurosurg. **16:** 551, 1959.
11. Bucy, P. C.: In Brennemann's Practice of Pediatrics, Hagerstown, Maryland, 1950, W. F. Prior Company, vol. 4, chap. 3.
12. Laurence, K. M.: The Natural History of Hydrocephalus, Lancet **2:** 1152, 1958.
13. Vickers, V. W., and Stuart, H. C.: Anthropometry in the Pediatrician's Office, J. PEDIAT. **22:** 150, 1943.

Anterior fontanel bone

(Report of a case)

Webster H. Brown, M.D.*

BALTIMORE, MD.

ANTERIOR FONTANEL bones are rare.[1] None was found by Henderson and Sherman[2] in 100 skulls of newborn infants subjected to intensive radiologic study nor were any seen in the films of 1,030 newborn infants carefully reviewed by Dedick and Caffey.[3] In a later study by Caffey[4] the series had grown to 3,800 skulls of newborn infants and still not one anterior fontanel bone had been encountered. Finally, in the third edition of Caffey's *Pediatric X-Ray Diagnosis*[5] one example of the anomaly is reproduced. The occurrence of such bones is mentioned in at least 2 other radiologic textbooks, that of Pendergrass, Schaeffer, and Hodes[6] and that of Ritvo.[7]

The usual fontanels are situated at the 6 angles of the 2 parietal bones. Accessory fontanels may appear in other locations; Scammon[8] stated that there were nearly 20 differently situated accessory fontanels. It is to be presumed that fontanel bones might develop in any or all of these sites. They have been seen most often in the lateral fontanels, at the anterior and posterior angles of the lateral margins of the parietal bones. Bones within the posterior fontanel at the junction of the sagittal and lambdoidal sutures are said to be not uncommon, but confusion arises here because separately ossifying segments of the upper margin of the occipital bone (inca or triquetral bone) can be mistakenly identified as posterior fontanel bones.

The anterior fontanel bone appears to be a true accessory bone, not a Wormian bone, which develops within the membranous structure of the fontanel. The time of appearance is not known. It has been called the os bregmaticum and the antiepileptic bone.[9]

The only illustration of an anterior fontanel bone we have been able to find in the American literature was reported in a 2½-year-old female, said to be normal.[5] At that time it was still unfused to either the frontal or parietal bones.

The example which came to our attention first was the case of a male child seen at the age of 6 months. He was referred for x-ray films of the skull because of the suspicion of premature synostosis. Examination by the referring pediatrician (Dr. Milton Markowitz) had revealed a normal child at birth. At 2 months the anterior fontanel was noted to be rather small and at 5 months it appeared to be closed on physical examination. At this time the head also appeared somewhat enlarged. The circumference of the head had increased from 13 inches at birth to 16½ inches at 5 months of age.

*Address, 11 East Biddle Street, Baltimore 2, Md.

Serial head measurements were as follows:

Birth		13	inches
2	months	15	inches
5	months	16½	inches
12	months	17¾	inches
15	months	18	inches
2	years	18¾	inches
2½	years	19¼	inches
3	years	19½	inches
4	years	20½	inches
5	years	20¾	inches

A posteroanterior film of the skull made at 6 months (Fig. 1) showed clearly all the major sutures and the accessory bone within the anterior fontanel.

A film made at the age of 22 months shows that fusion of this accessory bone within the anterior fontanel had taken place (Fig. 2). The infant had developed normally to this date.

Scammon[8] stated that the presence of an accessory fontanel bone may lead to earlier than normal closure of that fontanel. This was surely not the case in Caffey's example.[5] It seems clear that such bones may occur in otherwise normal infants and that they may fuse to adjacent bones after a variable period of time. No record of their remaining unfused to late childhood or adult life has been found.

A recent study by Aisenson[10] suggests that the anterior fontanel may close at an earlier date than older reports indicated. Closure was completed in his series at any time between 4 and 26 months; 2.7 per cent were completely closed by the age of 6 months, 13.5 per cent by the age of 9 months, and 91.3 per cent by 18 months. It is, therefore, possible that a fontanel which closes at 6 months or earlier might simulate a fontanel bone.

SUMMARY

A case demonstrating an anterior fontanel bone has been presented. This instance shows that the fontanel containing a fontanel bone may close well within the normal range of time. One author states that the anterior fontanel may close prematurely under these circumstances. Still another presents a case in which the bone is unfused after the usual closure time. Apparently there is great individual variation in closure of fontanels exhibiting this uncommon finding.

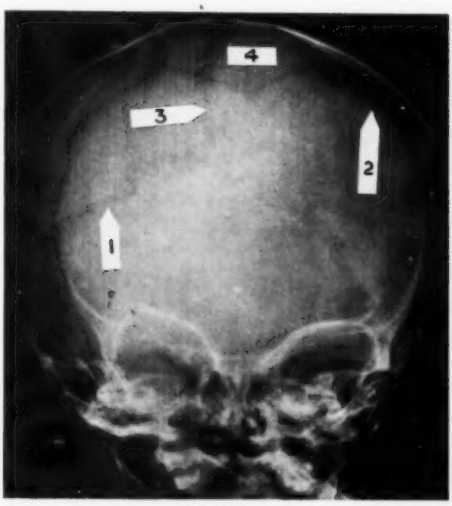


Fig. 1. Skull at age 6 months: (1) lambdoidal suture, (2) coronal suture, (3) sagittal suture, and (4) anterior fontanel bone.

Fig. 2. Skull at age 22 months: (1) sagittal suture and (2) fused anterior fontanel bone.

REFERENCES

1. Schuller, Arthur: Roentgen Diagnosis of Diseases of the Head. Authorized translation by Fred F. Stocking, M.D., M.R.C., St. Louis, 1918, The C. V. Mosby Company.
2. Henderson, S. G., and Sherman, Louise S.: The Roentgen Anatomy of the Skull in the Newborn Infant, Radiology **46:** 107, 1946.
3. Dedick, Andrew P., and Caffey, John: Roentgen Findings in the Skull and Chest in 1,030 Newborn Infants, Radiology **61:** 13, 1953.
4. Caffey, John: On the Accessory Ossicles of the Supra-occipital Bone. Some Newly Recognized Features of the Normal Infantile Skull, Am. J. Roentgenol. **70:** 401, 1953.
5. Caffey, John: Pediatric X-ray Diagnosis, ed. 3, Chicago, 1956, The Year Book Publishers, Inc.
6. Pendergrass, E. P., Schaeffer, J. P., and Hodes, P. J.: The Head and Neck in Roentgen Diagnosis, Philadelphia, 1956, W. B. Saunders Company.
7. Ritvo, M.: Roentgen Diagnosis of Diseases of Skull, vol. 19, Annals of Roentgenology, New York, 1949, Paul B. Hoeber, Inc.
8. Scammon, R. E.: A Summary of the Anatomy of the Infant and Child, in Abt, I. A., editor: Pediatrics, Philadelphia, 1923, W. B. Saunders Company, vol. 1.
9. Dyke, Cornelius G., and Childe, Arthur E.: Roentgen-Ray Diagnosis of Disease of the Skull and Intracranial Contents, in Golden, Ross, editor: Diagnostic Roentgenology, Baltimore, Williams & Wilkins Company, pp. 30A and 30C.
10. Aisenson, M. R.: Closing of Anterior Fontanelle, Pediatrics **6:** 223, 1950.

Head banging in early childhood

A study of incidence

Vladimir de Lissovoy, Ph.D.*

UNIVERSITY PARK, PA.

HEAD banging is a curious behavior pattern sometimes seen in infancy and early childhood. This activity consists of repetitive movements marked by a definite rhythm and monotonous continuity. The head is struck rhythmically against the headboard, side railing of the crib, or other objects. This is not a tantrum type of behavior but is marked by an almost compulsive repetitiveness. A systematic description of this behavior based on observations of head bangers is to be found in other publications.[1, 2]

Most of the references dealing with head banging describe its frequency with such words as "often," "frequent," and "common." The lack of statistical reference in judging incidence suggests caution in the use of these words for such behavior.

Lourie[3] found that 15 to 20 per cent of children in "an unselected pediatric clinic population" had "rocked, banged or swayed in one form or another for a longer or shorter time." He suggests that 10 per cent of the children seen in private practice manifest rhythmic behavior patterns. By contrast Margaret Mead[6] stated, "I have never seen a case of rhythmic behavior which you describe."

From the College of Home Economics, The Pennsylvania State University.

**Address, Associate Professor of Child Development and Family Relationships, College of Home Economics, The Pennsylvania State University, University Park, Pa.*

Levy and Patrick[4] studied the relation of headaches and fainting in mothers to infantile convulsions, head banging, and breath holding. Of a total of 422 children, 14 were head bangers (3.32 per cent); of these 10 were boys and 4 were girls.

The incidence of Negro children with rhythmic behavior patterns has been estimated by Roland Scott[5] to be 10 per cent of a hospital population.

This study attempts to establish the incidence of head banging in a population of normal, not hospitalized infants and young children.

SAMPLE AND METHODOLOGY

The sample consisted of 487 normal, full-term babies born in an upstate New York hospital during 1958. From the hospital records the date of birth, weight at birth, birth order, age of mother, and occupation of the father were obtained.

Mothers were contacted by mail. A letter explained the purpose of the study and a short questionnaire together with a return-addressed envelope was included. A total of 374 replies were received (76.8 per cent); of these 6 were not used. Two of the children had died since birth; 4 questionnaires left out most of the needed information. The data presented in this study are based upon a 75.5 per cent return of questionnaires. An

Table I. Incidence of head banging in 374 normal, not hospitalized children aged 19 to 32 months

	Boys (N = 198)	*Girls (N = 176)*	*Total (N = 374)*
Number of head bangers	44	13	57
Per cent of head bangers	22.3	7.4	15.2

examination of the sex distribution of the children whose mothers failed to return the questionnaire disclosed no bias in favor of either sex.

The questionnaire included two main questions:

1. Some children rock back and forth for a long period of time, either in their cribs or in bed. Usually children are on their hands and knees when they do this although other positions are commonly assumed. Did your child ever go through this stage?

2. In some cases a child will hit his head over and over against a pillow, the headboard, the side of the crib, or the back of the sofa. We do not mean bang his head on the floor in anger or in a tantrum, rather we mean a persistent, habitlike banging. Did your child ever go through this stage?

The mothers were also asked to indicate when rhythmic behavior was first noted and to indicate if the child at the present time rocked or banged his head.

The question regarding crib rocking was included because Lourie[3] had noted these two behavior patterns to be concomitant. Also, in a previous study[1, 2] this investigator noted that crib rocking or other rhythmic behavior consistently preceded the onset of head banging.

RESULTS

It will be noted from the data in Table I that boys tend to exceed girls in the total sample and that 57 children, or 15.2 per cent, were or had been head bangers. The prevalence of boys among head bangers has been noted by Lourie,[3] Levy and Patrick,[4] Kravitz,[7] and de Lissovoy.[1]

The average age of mothers of children who were head bangers was 26.22 years; mothers whose children did not follow this pattern of behavior averaged 27.40 years of age.

The occupation of fathers by Shartle's[8] classification:

Professional	5
Semiprofessional	2
Business, proprietors, and managers	6
Clerical	5
Crafts, operatives, and laborers	37
Students	2
Total	57

In addition to the 57 head bangers, 32 of whom were also identified by their mothers as crib rockers, 19 boys and 27 girls were crib rockers only. There was no difference in birth weight between boys who were rockers and those who were not. Girls who were "rockers only" were on the average 3 ounces lighter at birth than were nonrocking girls. An examination of birth weight of head bangers showed the differences noted in Table II.

It will be seen from the data in Table II that girls who were head bangers were, on the average, 8 ounces lighter at birth than were non–head-banging girls. This difference did not prevail in boys.

Table II. Birth weight of head bangers and non–head bangers by sex (average birth weight in ounces)

	Head bangers		*Non–head bangers*	
Boys	(N = 44)	119.25	(N = 134)	119.41
Girls	(N = 13)	109.23	(N = 136)	117.53

Table III. Months of age when head banging was first noted by mothers

Months	*Girls*	*Boys*
1-3	1	1
4-6	2	8
7-9	2	10
10-12	2	11
13-15	-	6
16-18	1	3
19 or over	5	5
Total	13	44

Fifteen of the head bangers were first born while 42 were last born into families with other children (chi square = 12.3, $p < .001$). This finding is contrary to the opinion of Spock,[9] ". . . the first baby in a family is more likely to bang his head. . . ." In a series of 30 head bangers I[1] found that 6 were only children, 1 was a middle child, 2 were first-born, and 21 were last-born children. Although it is not the purpose of this report to suggest correlates of head banging, available data indicate a prevalence of head banging among last-born children.

It was noted in my previous study[1] that head banging was preceded in all instances by other forms of rhythmic activity such as body rolling, head rolling, or crib rocking. The data in this study are not so clear-cut. Rocking activity was noted in 32 cases prior to head banging, but in 25 cases mothers indicated that no rocking had been noted prior to the onset of head banging. Of the children who were "rockers only" 15 were first-born children and 31 were last born at the time of this study (chi square = 5.6, $p < .02$).

It can be seen from Table III that 37 children were noted by their mothers to be head bangers prior to their first birthday. The last half of the first year appears to have been the period of onset most often noted by mothers in this sample of children. This finding is in accordance with previous observations.[1, 3, 9]

SUMMARY

On the basis of 75.5 per cent returns of questionnaires sent to mothers who gave birth to normal full-term babies in an upstate New York hospital during the year 1958, 57 children were identified by mothers as head bangers (15.2 per cent of the sample). Of these 44 were boys and 13 were girls. In addition to the children who were head bangers 46 were crib rockers only.

REFERENCES

1. de Lissovoy, V.: Head Banging in Early Childhood: An Exploratory Study of an Atypical Behavior Pattern, unpublished thesis, Cornell University, 1959.
2. de Lissovoy, V.: Head Banging in Early Childhood, Child Dev. (in press).
3. Lourie, R. S.: The Role of Rhythmic Patterns in Childhood, Am. J. Psychiat. **105:** 653, 1949.
4. Levy, D. M., and Patrick, H. T.: Relation of Infantile Convulsions, Head Banging and Breath Holding to Fainting and Headaches in the Parents, Arch. Neurol. & Psychiat. **19:** 865, 1928.
5. Scott, R. B.: Personal communication.
6. Mead, M.: Personal communication.
7. Kravitz, H., et al.: Reported in the Chicago Daily News May 3, 1960, p. 16.
8. Shartle, C.: Occupational Information, New York, 1952, Prentice-Hall, Inc.
9. Spock, B.: Baby and Child Care, New York, 1957, Pocket Books, Inc., p. 206.

Enuresis in children

Harry Bakwin, M.D.*

NEW YORK, N. Y.

ENURESIS is one of the most frequent and, at the same time, one of the most annoying disorders of childhood. It was recognized as a disturbance of children requiring treatment as early as 1550 B.C.[1] and has been commented upon repeatedly over the centuries.

Theories as to its nature vary with the fashion of the times. Among primitive peoples supernatural forces are invoked and treatment is designed to exorcise evil spirits. A method in use among the Bantu (Zulus) of South Africa is to scarify the skin over the cheeks and allow the "bad blood" to escape. Enuresis is regarded by some urologists as a symptom of organic defects in the urogenital tract, and they have demonstrated a number of abnormalities in the bladder and urethra in patients resistant to the usual therapeutic procedures. A view popular several years ago was that enuresis is an undesirable habit and represents persistence of an infantile form of behavior much like thumb sucking. More recently the psychiatrists have incorporated enuresis as an expression of an emotional disturbance and this view has been accepted widely.

DEFINITION

A major difficulty in defining enuresis is the variable age at which children achieve bladder control. The age depends on the developmental tempo, the training procedures, the personality make-up of the child, the emotional climate in the home, and a variety of incidental factors.

Developmental readiness for bladder training implies that the child can support himself on the toilet seat, that he has some awareness that his bladder is filled, that he can retain the urine until he is placed on the toilet, and that he can release the sphincters appropriately. He should also have some awareness of the social implications of the situation.

Obviously all these maturation phases do not emerge simultaneously. A child is able to sit alone at 6 to 8 months, many months before he can be expected to grasp, even vaguely, the reasons why urinary control is necessary. The ability to retain the urine is achieved before the ability to release the sphincters. It is probably too early to start bladder training as soon as the baby can sit and it is probably too late to wait until the meaning of the act is comprehended. An intermediate time, somewhere between 11 and 14 months, is the usual, arbitrary choice.

Training procedures obviously influence the time when control is attained. In this respect sphincter control differs from the motor and speech functions which unfold with little relation to training. It is said that some children train themselves, meaning that they achieve sphincter control by observing the behavior of others, but this is certainly not the rule.

From the Department of Pediatrics, New York University School of Medicine, New York, N. Y.

**Address, 132 East 71st Street, New York 21, N. Y.*

The response of the youngster to training will depend, to a considerable extent, on the emotional climate in the home. Parent-child conflicts, often centering about toilet training, rouse the child's negativism and may delay the establishment of regular toilet habits.

Equally important is the personality of the child. Some children are, for one reason or another, acquiescent, others resistant; some are of an adventurous nature and interested in new activities, others are cautious, approaching each strange situation hesitatingly. The training technique must be adjusted to the personality of the child.

Reports on the time when children attain bladder control differ widely. Macfarlane and associates[2] report continued night-wetting at 3 years in 18 per cent of boys and 31 per cent of girls. Klackenberg[3] found that only 13 per cent of his subjects were still wetting nights at 3 years and in Wallgren's[4] subjects night control was established even earlier. Klackenberg was unable to discern any connection between training and nocturnal bladder control, but this is not the experience of others.

The complexities of determining the age at which urinary control is attained are well illustrated in the study of Roberts and Schoellkopf.[5] They point out that the problem of when a child is trained is complicated by the extent to which the mother shares responsibility for control by picking up the youngster at night, by calling his attention to the need during the day, and so on. In their group of 2½-year-olds from middle-class families, 56 per cent were dry at night and about the same percentage during the day. About 40 per cent of this group either called the mother at night or were taken up automatically. Forty per cent of the children continued to wet more than twice a month at 2½ years.

Certain sex differences in urinary function were observed by Roberts and Schoellkopf at 2½ years. Infrequent wetting was reported by the mothers more often in girls than boys. Moreover, more girls than boys assumed responsibility for the act. Maternal reminding was necessary 4 times as often in boys as in girls. The authors point out that these differences do not necessarily relate directly to urinary function. Mothers tend to be more solicitous of boys and may permit girls more initiative in managing their toilet needs. Then, too, girls are more compliant than boys, needing less urging; in addition, mothers may be more fastidious about girls and help them earlier to be clean so that by the age of 30 months they are further advanced in this respect than boys.

In most reports children who continue to wet persistently after their third birthday are considered enuretic. This choice is arbitrary; without question an otherwise normal child will occasionally fail to attain control until later on.

THE CLINICAL PICTURE

Enuresis is to be distinguished from urinary incontinence in which bladder control is lost and the passage of urine is automatic. The enuretic subject is aware of bladder distention and can control its emptying but with greater difficulty than normal individuals.

The term enuresis should not be applied to the wetting and soiling frequently seen in young children following the birth of a sibling. They usually wet and soil while sitting on the mother's lap, they demand to be diapered, they want to suck at the bottle or breast, they make excessive demands to be held and fondled. Such behavior is part of a regressive reaction and is transient unless the child is constitutionally predisposed.

In the large majority of enuretic children night-wetting is continuous from infancy, bladder control never having been established. They wet nightly, often several times a night. The amount passed is usually copious. The habit may cease at any time during childhood—often at 6 to 8 years—but it generally continues until the early teens when it ordinarily corrects itself. A small percentage continue to wet in adult life.

A prominent symptom is urgency. The need to urinate is immediate and may be accompanied by acute discomfort, restlessness, abdominal pain, and, in some instances, dribbling and day-wetting.

The intensity of the urgency varies. Some children need relief as soon as the desire to urinate appears; others can wait a limited time. It may be that certain children become engrossed in play or other absorbing interest and put off emptying the bladder until the urgency is extreme. Psychological factors may also contribute; situations of a disturbing emotional nature may be expected to exaggerate the urgency in a predisposed child.

Urgency often persists throughout life after the bed-wetting has ceased. All degrees are seen in adults. It may be mild, manifesting itself only as an exaggeration of the normal response to excitement, cold or wet weather; or it may be intense and accompanied by nocturia or a continuation of enuresis.

Urinary frequency is often present. As a rule enuretic children are unable to sit through their school sessions without leaving the room. Even those without marked frequency generally go more often than usual. The normal person, when bladder fullness is experienced, puts off urination until such time as is convenient and consequently the number of visits to the toilet will be less than in the case of the enuretic whose waiting time is limited. Moreover the latter is apt to become tense when the need to urinate arises and this, as in the normal individual, increases bladder irritability.

Day-wetting—diurnal enuresis—frequently accompanies night-wetting. It was observed by Still[6] in over 40 per cent of his patients. Generally it occurs only occasionally but in about 10 per cent of such patients it takes place daily or several times a day. Like night-wetting, it is usually present from the beginning, the child never having attained day control. Day-wetting without night-wetting is unusual, accounting for less than 5 per cent of all the cases of enuresis.

There are a number of reasons why children wet themselves during the day. Nervous tension, from whatever cause, exaggerates the urgency characteristic of enuresis and in this way may lead to wetting the clothes. Unlike nocturnal enuresis, "nervous symptoms" and encopresis are more frequent in day-wetters than in normal children. It is not clear whether the nervous symptoms or the diurnal enuresis is primary. Day-wetting is also observed in shy children who are too timid to ask permission to leave the classroom for the toilet; in conscientious children who are afraid to leave the classroom lest they miss important work; in girls who are fearful of sitting down on a strange toilet; and in children who become so engrossed in play or other activities and wait so long that they are unable to reach the toilet in time. Probably there are innate differences in the intensity of the urgency.

In day-wetting without night-wetting the causes are the same, the only difference being that the child gets up during the night to empty the bladder and consequently does not wet the bed.

In a certain number of children (15 to 25 per cent of all cases) the enuresis appears after bladder control has been maintained for several years. Some of these children had been picked up during the night and placed on the toilet but this custom was discontinued. A common reason is that the child has entered school and the parents do not want to disturb his sleep. Unlike their normal peers, these children are unable to sleep through the night without emptying the bladder, but they are prevented from wetting the bed by being picked up. When they are left on their own they wet the bed.

There is, however, a small group for whom such a history cannot be obtained. These children seem to have been normal in every respect as far as bladder function is concerned until the bed-wetting began.

The future appearance of enuresis may be suspected in some infants when repeated episodes of ammoniacal dermatitis occur despite good care, and in boys with ulcerated meatus. In such instances the mothers often complain that the children are always wet and the frequency persists after the dermatitis has disappeared. Inquiry reveals, in many of these cases, that other members of the immediate family are enuretic.

Emotional status. In general the emo-

tional reaction to nocturnal enuresis is not severe, but children do worry about the stigma of being a bed-wetter, their inability to go visiting, their weak will in not being able to control urination, fear that it will continue into adult life and interfere with marriage. The attitude of the parents and siblings will, of course, influence the youngster's reaction. It is surprising how often parents, who were themselves enuretic during childhood, fail to understand the child's problems and apply coercion, punishments, threats, and shaming in an effort to rid him of his wetting. But even an accepting, understanding home atmosphere is not sufficient to allay concern entirely in a sensitive, intelligent child who appreciates the drawbacks of his difficulty.

The behavior of the child with nocturnal enuresis is in no way characteristic. Some respond with withdrawal and shyness, others with bravado, still others with accepting resignation. "Immature behavior" is frequently mentioned in the literature as characteristic of the boy with enuresis. We have not observed it.

Michaels and Goodman[7] concluded that 5 traits—enuresis, thumb sucking, nail biting, speech impediment, and temper tantrums—occur more often in combination than in isolation. They suggest that enuresis is the common indicator of this symptom complex and that it is a reflection of an ill-balanced personality rather than an independent, unrelated, and insignificant manifestation. They favor an innate predisposition to this type of symptom complex.

The material for their study was obtained from 475 summer campers, ranging in age from 6 to 19 years of age. The children came, dominantly, from "fairly comfortable homes." The data were based on the histories of the campers and in most instances the symptoms were no longer present at the time the histories were taken. Their findings have not been confirmed by other observers.

Hallgren,[8] basing his conclusions on a statistical survey, reported that behavior disorders, nervous symptoms, and speech disorders were more frequent in enuretic children than in either their unaffected or affected (with enuresis) siblings. The incidence of emotional disturbances was slightly higher in the children with day- as well as night-wetting. It was also somewhat more frequent in the children who acquired their enuresis after a period of normal urinary control. No relation to reading disability was found.

There was a significantly higher incidence of broken homes, maternal psychiatric disorders, and mother-child separation among enuretic children. Precipitating factors in the cases of acquired enuresis after a period of normal control were birth of a sibling and separation from the parents.

No appreciable differences in the responses of enuretic and control children to the Rorschach Test were found by Schachter and Cotte.[9]

Lapouse and Monk[10] were unable to discover a statistically significant correlation between a considerable number of fears and worries and the presence of enuresis.

Macfarlane and co-workers[2] found no significant relationship between wetting and other problems after 21 months of age.

It is of interest in this connection that enuresis is a common problem among children reared in the Kibbutzim or communal farms in Israel. The children are transferred to nurseries after birth and spend their entire childhood apart from their parents in groups under the direction of housemothers. They are visited by their parents from time to time and they also visit their parents' homes occasionally, sometimes for several days. Problem behavior, with the exception of enuresis and finger sucking, is said to be unusual.

In brief, then, no well-defined behavior differences are found in the children with enuresis. The minor changes reported in some studies (but not in all) might well be explained by the effect of the symptom on the child's behavior.

Deep sleep. This is frequently mentioned as an accompaniment of enuresis. This clinical impression is borne out by a number of studies. Hallgren,[8] on the basis of interviews

with the parents, reported that heavy sleep was more common in enuretic than in nonenuretic children and among affected boys than in girls. Some evidence was found that the deep sleepers continued to wet until a later age than the others.

Ström-Olsen,[11] in a study of 28 adults with enuresis, found that 25 had hypersomnia. As a group these individuals were free from anxiety, level-headed, stolid, placid, imperturbable, often dull. They fell asleep promptly on going to bed and their sleep was heavy and dreamless. Even in the morning, when normal sleep is usually light, they were hard to awaken. Amphetamine made their sleep more nearly normal, but they often required large doses—up to 30 mg.—at bedtime.

Macfarlane stated that, of girls at 21 months of age, it was the sound sleeper who wet the bed.

Ditman and Blinn[12] studied the electroencephalogram during sleep in 25 male subjects with enuresis, all but 4 of whom were naval recruits 17 years old or older. They concluded that enuresis in their group was not regularly associated with deep sleep. Their findings are unusual in that they, unlike other workers, found the electroencephalograms in their enuretic patients normal throughout.

Urine output. The view is held by a number of workers that in a sizable percentage of enuretic persons the urine is not concentrated at night in normal fashion. Friedell[13] in 1927 found that 8 out of 39 enuretic subjects passed urine of relatively low specific gravity at night. This group was particularly resistant to treatment. In 1953 Poulton and Hinden[14] reported that an unusually large quantity of urine was excreted at night by more than three-fourths of a group of 200 enuretic patients.

The subject was reinvestigated by Vulliamy[15] in 22 enuretic and 24 control children under standardized conditions of diet and fluid intake. No significant difference was found between the two groups. The average day-to-night ratio of urine output was 1.93 in the enuretic group and 1.90 in the control children. Four children showed nocturnal polyuria. Two were enuretic and 2 were controls.

Bladder capacity. Cystometric studies by a number of observers agree that the bladder capacity in enuretic persons is often small. The differences from the normal are, however, neither striking nor constant. For example, Diwani, Zaki, and Mouktar[16] describe normal cystometric curves in 56 per cent of their patients. Thirty-one per cent showed definitely small bladders. In 6 per cent, however, the bladders were hypotonic.

Hallman[17] studied the bladder capacity by comparing the output in enuretic and nonenuretic children after water drinking. Although there was considerable overlapping the output per urination was, on the average, appreciably smaller in the enuretic than in the nonenuretic children.

Electroencephalogram. Michaels and Secunda,[18] in the course of a study of the electroencephalogram in a group of children with various "neurotic" traits, discovered that, of all the children studied, those with enuresis showed the highest association with an abnormal EEG. The most frequent abnormal finding was a "wave of slow rate."

Gunnarsen and Melin[19] found abnormal electroencephalograms in 77 per cent of 62 children who had never been dry, and in 54 per cent of 26 children who had started to wet after a period of normal bladder control. The changes observed were slow or dysrhythmic EEG's, 3 to 5 per second large waves, often in the occipital regions. Sometimes general dysrhythmia was combined with hypersynchrony. They conclude that abnormal EEG's were more frequent in the group that had never been dry than in the group that started to wet after a period of normal bladder control but the difference between the two groups is of questionable significance ($p = 0.05$).

Turton and Spear[20] investigated 100 children with severe enuresis. In 49, the records were normal or nearly so. Of the remaining 51, 28 showed an excess of slow activity, which the authors interpret as evidence of

immaturity, and 8 showed abnormalities of an epileptiform nature. The changes were pronounced, but sustained seizure patterns were not observed. In a further 14, records pathognomonic of epilepsy were found with typical seizure patterns. Other children showed focal lesions in the temporal lobe (1 case) and a variety of other abnormalities.

Schaper[21] observed an increase in slow activity and other evidence of abnormalities in the electroencephalograms of enuretic children. Pierce and his collaborators[22] report 25 per cent abnormal electroencephalograms in 60 young adults with enuresis, versus 1.7 per cent in a control group.

Ditman and Blinn,[12] alone, report no electroencephalographic changes in enuretic subjects.

Urologic studies. Visualization studies of the bladder and urethra yield conflicting evidence. Campbell,[23] working with children resistant to the usual methods of treatment, found abnormalities in the urogenital tract which he considered causally related to the enuresis in two thirds of his patients. In girls the most frequent lesion was a urethrotrigonitis and in boys a congenital narrowing along the urethra, usually at the meatus. Other lesions were also found.

Cohen[24] described urologic changes in 22 of 25 adults with enuresis. Stockwell and Smith[25] and Brodny and Robins[26] also report abnormalities in an appreciable number of enuretic individuals.

Fisher and Forsythe,[27] using the cystourethrogram, studied 135 children 5 years old or older with persistent enuresis. The technique consists of injecting a radiopaque substance into the bladder and observing the residual urine, the bladder configuration, and the configuration of the urethra. Abnormalities were observed in 41 of 84 boys and in 20 of 51 girls. Twenty-five per cent of the boys had valves of the posterior urethra, and one showed stenosis of the membranous urethra. In 9, neurogenic bladder was present with either greatly increased bladder capacity or constricted and trabeculated bladders and smooth funnelling of the bladder neck. Other anomalies were found occasionally. Of the 20 girls with abnormalities, 3 had neurogenic bladder and 14 a wide bladder-neck anomaly. Two showed bladders of small capacity and one a unilateral reflux without other detectable lesion. The enuretic patients who had anomalies of the bladder and urethra were indistinguishable clinically from those with normal cystourethrograms.

In marked contrast to these reports are the urethrocystographic studies of Hallgren[8] on 105 children with enuresis. Twenty patients were further investigated by cystoscopy. Abnormalities were found in only 3 children, and these did not seem to be related to the enuresis.

It seems reasonable to conclude that anatomic changes in the urogenital tract are rare causes of enuresis in children. The large majority outgrow their symptoms and, except for urgency in some of them, live normal lives.

Spina bifida occulta. Over 50 years ago Fuchs[28] suggested that spina bifida occulta is related to enuresis. Though the idea has been repeatedly shown to be fallacious, x-ray examination of the lower spine is still frequently included in studies of children with enuresis.

Stalker and Band,[29] in 1946, reviewed the extensive literature on the subject and added fresh observations of their own. They concluded that variations in ossification of the lumbosacral spine such as fusion defects, lumbarization, and sacralization are common in normal persons and bear no relation to enuresis. Fusion defects disappear in the normal process of ossification.

Epilepsy. A relationship between enuresis and epilepsy was suspected by early students of enuresis. Renewed interest in this subject stems principally from electroencephalographic studies which show patterns compatible with epilepsy in a relatively high percentage of children with enuresis. Schaper[21] concluded, from a study of 100 enuretic persons, that a greater than expected number gave a history of febrile convulsions and epilepsy (grand mal, petit mal, absences). Relatives also showed more convulsive dis-

orders. A history of convulsions was more frequent in the wetters who had never had a dry period than in those who had. The wetters from birth also showed in the EEG an excess of slow activity as well as other abnormal findings indicating an increased irritability of the central nervous system.

DIFFERENTIAL DIAGNOSIS

The diagnosis of enuresis ordinarily presents no difficulties. The urine should always be examined because of the possibility of diabetes mellitus, diabetes insipidus, or infection of the urinary tract. Bed-wetting is occasionally a presenting symptom in epilepsy.

A congenital defect in the genitourinary tract should be suspected when the urinary stream is small, starting the stream is difficult, and dribbling is prominent. Dribbling alone is not infrequently present in enuresis.

Involuntary micturition may be a symptom of disease of the central nervous system.

INCIDENCE

Figures on the incidence of enuresis vary widely. The conflicting data are due to differences in defining enuresis, principally as to the age at onset and the frequency of wetting; differences in the age groupings; differences in the source of material, whether from the general population or from child-guidance clinics; and socioeconomic-ethnic differences.

It is generally agreed that socioeconomic status influences the frequency of bed-wetting. In the study of Blomfield and Douglas,[30] the incidence was lowest among children of the relatively prosperous professional and salaried groups and among the children of agricultural workers, and it was highest among the children of manual workers. The children of black-coated (or white-collared) workers formed an intermediate group. The discrepancy between the social groups widened with increasing age. At 7¾ years there were twice as many wetters among the poorer group as among the better off.

Socioeconomic differences in the frequency of enuresis are best understood if due consideration is given to the central role of urgency. The dominant feature in enuresis is the urgent need to empty the bladder when it is filled. If a child with urgency gets up at night and goes to the toilet he is considered normal. If he fails to answer the call promptly, enuresis supervenes. Whether or not he wets the bed depends on a number of incidental considerations. Such a child will be less likely to wet the bed if he comes from a home where cleanliness is prized, where the toilet is close at hand, where the mother is solicitous and takes special pains with toilet training, where the fluid intake before bedtime is regulated, where the youngster is picked up during the night to empty the bladder. On the other hand the likelihood of wetting is increased in a predisposed child if he resides in a home where habits of cleanliness are poorly developed, if he sleeps with a sibling who wets the bed, if the toilet is not readily accessible, if the home is cold at night, if he is excessively fearful, if he is a deep sleeper.

An appreciation of these factors explains, in part at least, the oft-mentioned socioeconomic distribution of enuresis. Children with the enuretic constitution are much more likely to wet the bed when the home is carelessly run than when it is neat and orderly.

There are, too, socioeconomic and ethnic differences in the willingness of parents to admit that their child wets the bed. Better-off parents tend to look upon bed-wetting as a mark of negligence and try to conceal it, while poorer families, in general, take it as a matter of course and discuss it freely. An exception among the poorer groups are Jewish parents, who are apt to deny enuresis because they regard it as implying poor home hygiene. Among educated groups, American parents seem more willing to discuss the symptom than the foreign born.

In the study of Michaels and Goodman,[7] enuresis was more frequent among the non-Jewish than among the Jewish children; and this was also the experience of D. Levy,[31] although other problems, notably eating and sleeping problems, were more frequent

among the Jewish children. Levy attributes the lower incidence of bed-wetting in the Jewish children to greater maternal solicitude and hence greater attention to toilet training. As further evidence of the role of training he points to the infrequency of enuresis in his carefully selected cases of overprotected children.

In most reports on the incidence of enuresis, boys predominate. Blomfield and Douglas[30] found that the higher frequency in boys is related to the socioeconomic status. In their study the preponderance of males was statistically significant only in the more prosperous families and not in the families of manual workers. Presumably, this difference is related to the greater neatness of girls and their readier response to training procedures.

FAMILY INCIDENCE

It is an old observation that enuresis is a family disorder, occurring with high frequency in the parents, siblings, and other near relatives of patients.

In Frary's[32] study, 32 per cent of the fathers and 20 per cent of the mothers gave a history of enuresis in childhood. Frequencies of the same order—39 per cent of fathers and 23 per cent of mothers—were obtained by Hallgren.[8] Stockwell and Smith[25] reported that 63 of 100 parents had had enuresis. If only one parent was affected in each case, then in 31.5 per cent of the cases a parent had had enuresis. Our data would indicate that, in a sizable percentage of cases, both parents had been enuretic. This would, of course, reduce the percentage of cases in Stockwell and Smith's series with an enuretic parent.

In our experience many parents are reluctant to admit that they were bed-wetters in childhood. A common reply to the question: "Did you have this trouble when you were a child?" or "At what age did you stop wetting the bed?" is, "I don't remember," or "I'll have to ask my mother."

In order to minimize errors in history taking from this source, we have surveyed a group of medical colleagues and, in addition, a small number of patients seen in private practice with whom a confidential relationship had been established.

Table I. Family incidence of enuresis

	No. of cases	*%*
Enuresis in one or both parents	18	72
Father	14	56
Mother	9	36
Both	5	20
Enuresis in neither parent	7	28
Total	25	100
Enuresis in siblings	17/43	40

Colleagues were asked, "Do—or did—any of your children wet the bed after their fourth birthday?" When a positive response was obtained, the inquiry was further extended to the frequency of wetting in the propositus, the incidence among the parents and the siblings, the age at which enuresis ceased, and the persistence of urgency.

Even in the present survey a certain number of wives replied that they did not remember about bed-wetting in childhood and would have to ask their mothers. These answers may well have been honest, since, in many of the medical colleagues' families, the enuresis ceased early in childhood at 6 to 8 years.

When the response was that none of the children wet the bed the question was asked, "Were you yourself or your wife (or husband) a bed-wetter in childhood?"

Twenty-five families in which at least one child was enuretic were surveyed. Nine of these were patients, the remainder colleagues. The results are shown in Table I. Of the 50 parents, 23 (46 per cent) had been enuretic during childhood. In 18 of the 25 families (72 per cent) at least one parent had been enuretic. In 5 families both parents had been bed-wetters. It is of interest that, in these 5 families, not all the children were enuretic. In only 7 cases (28 per cent) did neither parent give a history of enuresis. In one of these the child ceased wetting at 4¼ years following a severe attack of measles and remained dry thereafter. In another child without such a family history the wetting ceased at 4½ years.

In one family it was possible to trace the enuresis through 4 generations. A maternal great-grandmother had a "weak bladder." Both maternal grandparents had been enuretic. The maternal grandmother wet herself when she was 16 years of age while at a high school festivity and throughout life continued to lose some urine when she laughed heartily. The mother was a bed-wetter until 12 years of age. A maternal aunt was enuretic until 7 to 8 years and, as an adult, had difficulty in controlling the bladder when moved to laughter.

Of the 43 siblings of the enuretic children 4 years old and over, 17 (40 per cent) gave a history of enuresis.

In a series of 18 families (all medical colleagues) in which none of the children were enuretic, 3 parents (17 per cent)—2 fathers and a mother—gave a history of enuresis.

The high incidence of bed-wetting during childhood among the parents of children with this symptom points strongly to a hereditary basis for enuresis. In the educated, upper-income groups studied, family habit or family custom can hardly explain the high family incidence. Moreover, in 9 of the 25 families the fathers only, and not the mothers, gave a history of enuresis. It is not customary for a father to tell his wife, who has most to do with toilet training the children, that he was a wetter during childhood. The paternal enuresis, therefore, can hardly be expected to influence the mother's training procedures.

Moreover, "family custom" is eliminated in the children reared in Kibbutzim away from their parents. Dr. Mordecai Kaffman, in a personal communication, reports that, among 89 enuretic Kibbutz children, he found a significantly higher prevalence of enuresis in other members of the family than in nonenuretic children. One of every 4 enuretic children had a sibling who was a bed-wetter. Only parents of enuretic children gave, spontaneously, a history of enuresis in their own childhood. In one family, for 3 generations, all the female members had enuresis until the age of 8 to 12 years.

Studies in twins also bear out the view that enuresis has a structural basis. Hallgren[33] assembled the available data in the literature. Of 30 pairs of uniovular twins, 21 were concordant in regard to enuresis and 11 were discordant. All 10 pairs of binovular twins were discordant.

PATHOGENESIS

Almost as many hypotheses as methods of cure have been proposed to explain why children wet the bed. Pototsky,[34] writing in 1920, divided enuretic patients into the hyperexcitable or neuropathic, the hypobulic or psychopathic, and the intellectually and emotionally moronic. Others have attributed enuresis to local irritation, endocrine disturbance, urinary abnormalities, myelodysplasia, nocturnal polyuria, acid urine, and a host of other conditions.

Anderson,[35] on the basis of an extensive review of the literature—he lists 199 references—and his own observations, concludes that emotional factors constitute by far the largest group of elements in the causation or, at least, the continuation of enuresis. Physical factors are significant in a limited number of cases, as is habit training. Previous illness may also be causative, mainly through relaxation of habit training. Adverse features frequently met with in cases of enuresis were parental maladjustments, parental "failure" and "severity," sibling rivalry, feelings of inferiority, infantile traits, timidity, and sensitivity.

A psychiatric basis for enuresis has been advocated by Gerard.[36] In a widely quoted paper she described her experiences with 46 children who had been referred to a psychiatric clinic because of enuresis. In all cases, she reported, enuresis was only one of several neurotic symptoms. The boys were, consistently, passive, retiring, and self-depreciatory. Active play was avoided from fear of self-injury. They were dawdlers in such daily activities as dressing, eating, working in school, and they demanded more than the usual amount of help and assurance in performing tasks. Their school achievement was below expectation from their intelli-

gence levels and they were inattentive and easily distracted.

The enuretic girls were more nearly normal in their manifest behavior. They were leaders, independent and proficient, honest and frank. At school they were attentive, ambitious, and well-behaved. They were strongly competitive toward boys in play. Although fearless in daytime activities, they shared with the boys a common anxiety, nocturnal fear. Nightmares were frequent in both sexes.

Gerard proceeds to interpret her observations, mainly from intensive psychoanalysis of 6 cases. The remaining 40 were studied in less detail but, she considers, sufficiently long to discern the "neurotic" pattern. She ascribes the boys' behavior to a fear of women, whom they regarded as dangerous persons capable of injuring or destroying them if they themselves were active. To overcome this fear, they identify with women in the form of a passive attitude and an avoidance of the active role of the male. Urination is conceived of as a passive act, the urine being allowed to flow uncontrolled.

In girls, Gerard reported that fear of man as a destructive aggressor who could injure them was prominent. They "avoided the difficulty by denying men their abilities, eliminating them from their existence in fantasy, and yet identifying with the active male rather than the passive female." Whereas urination represents a passive flow in the male, it represents an active destructive process in the female.

Gerard hypothesizes that enuresis acts as a substitute for masturbation associated, in the female, with fantasies of activity, in the male with fantasies of passivity. She attributes the cessation of enuresis at puberty to the growth in sex interest and, consequently, the frequent practice of masturbation at this age period, thereby eliminating the need for the substitute activity of enuresis.

Gerard's studies are open to criticism on several lines. Estimates of personality are highly subjective. They would have meaning only if comparisons were made with a proper control group, the investigator not being aware of whether he was assessing a normal or an enuretic child.

The interpretations were based on a small number of enuretic children. The propriety of making generalizations about this everyday disorder from a group willing to undergo psychoanalysis is doubtful.

That enuresis is a substitute for masturbation is an assumption without corroborating data. It is true that enuresis generally ceases at about the time when masturbation increases but this by no means indicates a causal relationship. Moreover, Hallgren[8] found that masturbation was somewhat more frequent in enuretic children than in a control group.

Enuresis as a developmental disorder. The striking family incidence of enuresis points strongly toward a structural basis for this everyday disorder. Further evidence is found in the studies of twins, which show a much higher degree of agreement among uniovular than among binovular twins.

The basic defect in the enuretic individual is difficulty in inhibiting the mechanisms which have to do with emptying the bladder. McLellan,[37] basing his statements on cystometric studies, describes two types of abnormality in bladder behavior in response to the introduction of fluid. One or the other was present in all his subjects with severe enuresis. The first type was characterized by uninhibited rhythmic contractions of the detrusor occurring after the injection of 25 to 75 c.c. of fluid, increasing in amplitude until the bladder was filled, at which point there was an urgent need to empty it. The second type of abnormality was a smooth curve until bladder capacity was reached, at which point emptying it became imperative. Similar alterations of bladder function were observed by Stockwell and Smith[25] and by Forsythe and Karlan.[38]

The characteristic clinical manifestation of these abnormalities in bladder function is urgency. Unlike the normal person, who can wait for hours when his bladder is filled, the enuretic has an immediate need to empty the full bladder. The urgency may or may not be accompanied by bed-wetting.

If the child gets up at night to empty the bladder, he will not be included as a bed-wetter. If he fails to answer the call, he will be listed as enuretic.

Spontaneous improvement takes place during the second decade, but urgency of varying degree often persists throughout life.

Available data fail to demonstrate any defect in renal function. The urine constituents are normal, the relation of the day to the night urine is unaltered, according to Vulliamy's[15] careful studies, and the specific gravity is unchanged.

Structural defects in the urogenital tract have been described but they are found only occasionally and their relation to the symptoms is doubtful. Equally severe cases show no changes.

The bladder has, on the average, a smaller capacity than that of control children but there is much overlapping. Moreover, bladder capacity is not fixed but depends on extraneous factors. In normal individuals bladder capacity may be greatly reduced by cold weather or by intense excitement. The larger bladder capacity of the normal individual may simply reflect his ability to tolerate bladder filling, in sharp contrast to the enuretic person who reacts promptly to a full bladder.

Like the disorders in the language functions of speaking, reading, and spelling, enuresis may be suitably included under the general designation of a developmental defect. It is a common familial deviation which tends to improve spontaneously during the second decade.

A similar view has been expressed by Gesell and Ilg,[39] who speak of children who are "intelligent and well constituted emotionally yet they are backward and inept in sphincter control. It is almost as though they were handicapped by a specific disability (like constitutional poor spelling). The difficulties so transparently have a developmental origin that they should be guided on that basis."

Denny-Brown[40] also regards persistent enuresis as a manifestation of an "inborn, fixed difficulty in inhibiting bladder [contraction] after the bladder is distended beyond a certain volume of contents."

Again, as in the case of the language functions, enuresis may represent a developmental abnormality or, simply, a developmental delay. The persons in whom the urinary symptoms of urgency, nocturia, and enuresis persist throughout life probably display a developmental abnormality, whereas those who, once having achieved bladder control, are free of symptoms manifest a developmental delay. In each group, a family history of enuresis can usually be elicited.

It is of interest that most of the enuretic children of medical colleagues fell into the "developmental delay" group. Enuresis generally ceased at 6 to 8 years and residual symptoms were unusual in both children and parents. The patients who were referred because of enuresis, on the other hand, had symptoms which persisted longer, and a history of residual urinary symptoms in the parents was much more frequent. Presumably, this latter is the type which generally comes to the physician's attention.

It is possible that, in a certain number of cases based upon a developmental delay, enuresis continues as an undesirable habit after the developmental lag has been overcome. Poorly developed hygiene in the home may favor its continuance.

TREATMENT

Interview with the parents. The first step in the treatment of a child with enuresis is an explanation to the parents of the nature of the disorder. They should know that the wetting is due to an inborn deviation, that it is inherited from one or both of them, and that it is due to no fault or weakness on his or her part. Scoldings, shamings, threats, and punishments are unfair, unkind, and generally useless. Instead, a spirit of cooperation and helpfulness should be encouraged. In addition, the widespread distribution of enuresis should be pointed out and the usually favorable outcome stressed.

Some parents, influenced by current psychiatric theory, have the idea that this everyday problem is a symptom of an un-

derlying emotional disorder and that they themselves are responsible for their child's difficulty. Consequently they feel guilty. Then, too, since they regard the wetting as the child's way of releasing his pent-up emotional tensions, they believe that treatment of the enuresis alone would be inadequate and would result in his seeking other ways of expressing his unhappiness. A brief discussion, designed to relieve feelings of guilt and futility, is gratefully received by them.

While talking with parents, the physician should be alert to their personalities, their reactions to one another, and their reactions to the patient. Corrective suggestions are made as indicated.

Interview with the child. The patient should be included in discussions with the parents. Conversations with him are designed to rid him of feelings of inadequacy, shame, and guilt and to bolster self-confidence. Special stress is placed on the great frequency of enuresis and on its favorable outcome. The child should be made to feel that physician and parents are working with him to terminate the habit and that his active cooperation, in getting up at night to empty his bladder, in limiting fluids before bedtime, will be helpful.

While treatment is in progress it is wise to limit discussion at home about the wetting to an occasional word of encouragement and reassurance as improvement progresses.

Conditioning. The most effective means of treating bed-wetting is a conditioning device. This consists of a pad attached to an electric bell which rings as soon as the youngster starts to void. The device is suitable only for children who are mature enough to comprehend what is being attempted and who are willing to cooperate. It is most useful in children 8 years old or older with whom the situation can be discussed, but occasionally a bright child of only 6 years will be able to cooperate. When negativism or bravado ("I don't care if I do wet the bed") has developed, these attitudes should be handled in discussions before the apparatus is used.

About 90 per cent cures have been reported by Seiger,[41] and others have had similar success. Improvement ordinarily takes place in a few days. When relapses occur the apparatus must be used again. No undesirable emotional effects have been observed as a result of such treatment.[42]

Belladonna. Belladonna is the only one of the many drugs recommended for the treatment of enuresis which has survived. Even when not curative, it is helpful in the large majority of cases. It is especially useful where urgency and diurnal wetting are prominent.

Since the introduction of the conditioning device, belladonna should be reserved for children who are too young to use the conditioning device or who are resistant, for patients with marked urgency and diurnal enuresis, and for those who fail to respond to conditioning. It may be used in conjunction with the conditioning apparatus.

In order to be effective, belladonna must be given in adequate dosage. A safe initial dose for a 5-year-old child is 5 drops of the tincture (one drop is equivalent to 1/3,000 grain or 0.02 mg. of atropine) 3 times a day. The amount is increased daily by 1 drop per dose. Large amounts, up to 20 or 30 drops or more 3 times a day, are well tolerated by most children with enuresis. The earliest sign of intolerance is flushing, which appears 20 to 30 minutes after administration.

With doses of 10 to 15 drops of the tincture, 3 times a day, the first effect is a lessening of the urgency and the day-wetting. Further improvement may be expected as the dosage is increased. A second effect is a reduction in the amount of urine passed during the night. The dosage is increased until a therapeutic or toxic effect takes place.

Belladonna is continued for 8 to 10 weeks after improvement has become established. To avoid habituation the drug is omitted one day a week.

Experimental data on the effect of atropine on bladder function in animals have been reviewed by Amberg and Grob.[43]

In their own studies they observed a definite lowering in bladder pressure in 9 of 19 enuretic patients following the hypodermic injection of 1/100 to 1/150 grain of atropine (0.6 to 0.4 mg.).

In addition to its effect on bladder function, belladonna, by relieving the urgency, makes the patient more confident of his ability to hold his urine. In this way some of the tension, which increases bladder irritability, is reduced.

Training is helpful in the treatment of enuresis. It should be combined with belladonna administration and with the suggestion and assurance that treatment will be successful. Fluids are limited in the late afternoon and a dry supper given. When fluids are demanded, charged water, which is ordinarily drunk in small amounts, may be given. During the day, an attempt may be made to increase bladder capacity by voluntarily retaining urine as long as possible.[44] The value of this device is doubtful.

The child is awakened once or twice a night to void. He should be waked up fully since putting a half-asleep child on the toilet is useless as a training procedure.

Urologic study is indicated only when disease of the urogenital tract is suspected. If emotional problems are prominent, psychiatric aid may be helpful.

REFERENCES

1. Glicklich, L. B.: An Historical Account of Enuresis, Pediatrics **8:** 859, 1951.
2. Macfarlane, J. W., Allen, L., and Honzik, M. P.: A Developmental Study of the Behavior Problems of Normal Children Between 21 Months and 14 Years, Berkeley, 1954, University of California Press.
3. Klackenberg, G.: Primary Enuresis: When Is a Child Dry at Night? Acta paediat. **44:** 513, 1955.
4. Wallgren, A.: Functional Development During Infancy, Acta paediat. **38:** 637, 1949.
5. Roberts, K. E., and Schoellkopf, J. A.: Eating, Sleeping and Elimination Practices of a Group of Two and One-Half Year Old Children, A. M. A. Am. J. Dis. Child. **82:** 144, 1951.
6. Still, G. F.: Common Disorders and Diseases of Childhood, ed. 3, London, 1915, Oxford Medical Publications, p. 775.
7. Michaels, J. J., and Goodman, S. E.: Incidence and Intercorrelations of Enuresis and Other Neuropathic Traits in So-Called Normal Children, Am. J. Orthopsychiat. **4:** 79, 1934.
8. Hallgren, B.: Enuresis, a Clinical and Genetic Study, Acta psychiat. et neurol. scandinav. (supp. 114) **32:** 1, 1957.
9. Schachter, M., and Cotte, S.: Les enfants énurétiques, Ztschr. f. Kinderpsychiat. **8:** 102, 1941.
10. Lapouse, R., and Monk, M. A.: Fears and Worries in a Representative Sample of Children, Am. J. Orthopsychiat. **29:** 803, 1959.
11. Ström-Olsen, R.: Enuresis in Adults and Abnormality of Sleep, Lancet **2:** 133, 1950.
12. Ditman, K. S., and Blinn, K. A.: Sleep Levels in Enuresis, Am. J. Psychiat. **111:** 913, 1955.
13. Friedell, A.: A Reversal of the Normal Concentration of the Urine in Children Having Enuresis, Am. J. Dis. Child. **33:** 717, 1927.
14. Poulton, E. M., and Hinden, E.: The Classification of Enuresis, Arch. Dis. Childhood **28:** 392, 1953.
15. Vulliamy, D.: The Day and Night Output of Urine in Enuresis, Arch. Dis. Childhood **31:** 439, 1956.
16. Diwani, M., Zaki, A. A., and Mouktar, N.: Cystometric and Radiological Studies on Enuresis, Gaz. Egypt. Ped. Assoc. 1960.
17. Hallman, N.: On the Ability of Enuretic Children to Hold Urine, Acta paediat. **39:** 87, 1950.
18. Michaels, J. J., and Secunda, L.: The Relationship of Neurotic Traits to the Electroencephalogram in Children With Behavior Disorders, Am. J. Psychiat. **101:** 407, 1944.
19. Gunnarsen, S., and Melin, K. A.: The Electroencephalogram in Enuresis, Acta paediat. **40:** 496, 1951.
20. Turton, E. C., and Spear, A. B.: Electroencephalographic Findings in 100 Cases of Severe Enuresis, Arch. Dis. Childhood **28:** 316, 1953.
21. Schaper, G.: Hirnelecktrische Untersuchungen bei 100 Enuretikern, Ztschr. f. Kinderh. **77:** 141, 1955.
22. Pierce, C. M., Lipcon, H. H., McLary, J. H., and Noble, H. F.: Enuresis: Clinical, Laboratory, and Electroencephalographic Studies, U.S. Armed Forces M. J. **7:** 208, 1956.
23. Campbell, M. F.: A Clinical Study of Persistent Enuresis, New York J. Med. **34:** 190, 1934.
24. Cohen, D. L.: Nocturnal Enuresis in the Adult Male: A Urologic Study, J. Urol. **57:** 331, 1947.
25. Stockwell, L., and Smith, C. K.: Enuresis: A Study of Causes, Types and Therapeutic Results, Am. J. Dis. Child. **59:** 1013, 1940.
26. Brodny, M. L., and Robins, S. A.: Enuresis; the Use of Cystourethrography in Diagnosis, J. A. M. A. **126:** 1000, 1944.
27. Fisher, O. D., and Forsythe, W. I.: Micturating Cysto-urethrography in the Investigation of Enuresis, Arch. Dis. Childhood. **29:** 460, 1954.

28. Fuchs, A.: Über den klinischen Nachweis kongenitalen Defektbildungen in den unteren Rückenmarkabschnitten (Myelodysplasie), Wien. med. Wchnschr. **59:** 2142, 1909.
29. Stalker, H., and Band, D.: Persistent Enuresis: a Psychosomatic Study, J. Ment. Sc. **92:** 324, 1946.
30. Blomfield, J. M., and Douglas, J. W. B.: Bed-Wetting, Prevalence Among Children Aged 4-7 Years, Lancet. **1:** 850, 1956.
31. Levy, D.: Discussion of Michaels and Goodman, Am. J. Orthopsychiat. **4:** 103, 1934.
32. Frary, L. G.: Enuresis; a Genetic Study, Am. J. Dis. Child. **49:** 557, 1935.
33. Hallgren, B.: Nocturnal Enuresis in Twins, Acta psychiat. et neurol. scandinav. **35:** 73, 1960.
34. Pototsky, C.: Zur Behandlung der Enuresis nocturna, Deutsche med. Wchnschr. **46:** 180, 1920.
35. Anderson, F. N.: The Psychiatric Aspects of Enuresis, Am. J. Dis. Child. **40:** 591, 818, 1930.
36. Gerard, M.: Enuresis: A Study in Etiology, Am. J. Orthopsychiat. **9:** 48, 1939.
37. McLellan, F. C.: The Neurogenic Bladder, Springfield, Ill., 1939, Charles C Thomas, Publisher.
38. Forsythe, W. I., and Karlan, S. C.: Enuresis in Young Male Adults, J. Urol. **54:** 22, 1945.
39. Gesell, A. L., and Ilg, F. L.: The Infant and Child in the Culture of Today, New York, 1943, Harper & Brothers, p. 332.
40. Denny-Brown, D., and Robertson, E. G.: On the Physiology of Micturition, Brain **56:** 149, 1933.
41. Seiger, H. W.: Treatment of Essential Nocturnal Enuresis, J. Pediat. **40:** 738, 1952.
42. Behrle, F. C., Elkin, M. T., and Laybourne, P. C.: Evaluation of a Conditioning Device in the Treatment of Nocturnal Enuresis, Pediatrics **17:** 849, 1956.
43. Amberg, S., and Grob, O.: The Effect of Atropine on the Bladder of the Child, Am. J. Dis. Child. **41:** 507, 1931.
44. Herman, C.: Treatment of Enuresis by Reeducation, Arch. Pediat. **27:** 600, 1910.

Studies of respiratory physiology in children

V. Total lung diffusion, diffusing capacity of pulmonary membrane, and pulmonary capillary blood volume in normal subjects from 7 to 40 years of age

Giovanni Bucci, M.D., Charles D. Cook, M.D.,* and Herbert Barrie, M.D.,

With the technical assistance of Joanna F. Hamann

BOSTON, MASS.

THE exchange of oxygen and carbon dioxide by the lungs involves diffusion of the gases across the pulmonary membrane and diffusion and chemical combination within the pulmonary capillary blood. Few data on the total diffusing capacity of the lungs of children are available. Furthermore, there is little information about the diffusing capacity of the pulmonary membrane or about the pulmonary capillary blood volume in relation to age and body size. This report presents such data for normal children, adolescents, and adults ranging in age from 7 to 40 years. The single-breath carbon monoxide method of Krogh as adapted by Forster and co-workers[1] has been used for these measurements.

From the Department of Pediatrics, Harvard Medical School, and the Department of Medicine of the Children's Hospital Medical Center, Boston, Mass.

Supported by Grants E-1170 and H5339 from the National Institutes of Health, United States Public Health Service

**Address, The Children's Hospital Medical Center, 300 Longwood Avenue, Boston 15, Mass.*

This study was undertaken not only to provide data for normal subjects of various sizes, but more particularly to provide a basis for comparisons of values obtained in various pulmonary and cardiovascular abnormalities. The results of observations in patients with congenital and acquired heart disease will be the subject of other reports.[2]

SUBJECTS AND METHODS

Total lung diffusion for carbon monoxide (D_{LCO}) was measured in 59 subjects of whom 39 were male and 20 female. Forty-two of the subjects, who ranged in age from 7 to 40 years, were healthy volunteers and the remainder were children who were hospitalized for conditions which did not affect their growth, chest and lungs, or cardiovascular status. Twenty-four of the subjects were between 7 and 12, 19 between 13 and 18, and 16 between 19 and 40 years of age. Only 4 of the volunteers were trained subjects. Cardiopulmonary normalcy was established in the subjects by history, physical examination, and in some cases by a chest x-ray.

None of the adolescents or adults had smoked within 3 hours of the tests.

Lung volumes were measured in all subjects by spirometry combined with the closed-circuit helium dilution technique described in a previous report.[3]

The apparatus used for the determination of D_{LCO} differed in only a few details from that described by Ogilvie and co-workers.[4] A special four-way valve with a dead space of only 25 ml. allowed the operator to connect the patient to (1) the bag-box source of the gas mixture, (2) the spirometer system, (3) complete obstruction, and (4) the collection bag. Position No. 3 proved particularly useful during the breath-holding period in working with children. A rotational potentiometer connected to the spirometer and recording on a direct-writing oscillograph allowed accurate timing of the period of breath holding. The period was considered to start at 50 per cent of the inspiratory volume and to end at the beginning of the sample collection. In the actual determination of D_{LCO}, the subject was connected to the spirometer system, performed 6 to 8 deep respirations followed by a maximal expiration and then took as rapidly as possible a maximal inspiration of gas containing approximately 0.3 per cent carbon monoxide, 10 per cent helium, 21 per cent oxygen, and 68.7 per cent nitrogen. The breath was held for approximately 10 seconds and the subject instructed to make a maximal expiratory effort as rapidly as possible. The collected sample was discarded if the spirometer recording indicated that a volume of gas less than three times the

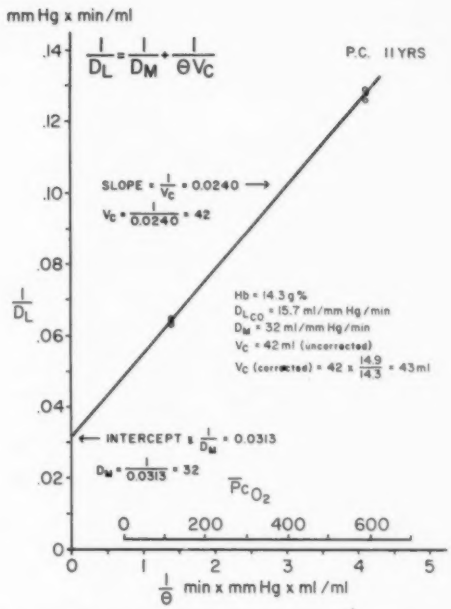


Fig. 1. Results of diffusion studies in one patient showing calculation of D_M and V_c.

estimated total dead space had been washed out and every effort was made to collect only the last portion of the expired gas. At least 2, and usually 3, determinations of D_{LCO} were made at 10 minute intervals.

Roughton and Forster[5, 6] have demonstrated that the total diffusing capacity of the lungs for carbon monoxide is the result of two components: (1) the diffusing capacity of the pulmonary membrane (D_M) and (2) the rate of uptake of CO by the blood in the pulmonary capillaries (θV_c). V_c is the total amount of blood present at any instant in pulmonary capillaries perfus-

Table I. Per cent variations in D_{LCO} determinations (34 studies in 30 normal subjects)

	High O_2 tension			*Low O_2 tension*		
Determination	1st	2nd	3rd	1st	2nd	3rd
Average variation in D_{LCO}*	+4.1	− .3	−3.8	+2.1	−1.2	− .9
Standard deviation*	±4.7	±3.6	±3.8	±4.0	±2.5	±2.5
Comparison between averages	1st and 2nd	1st and 3rd	2nd and 3rd	1st and 2nd	1st and 3rd	2nd and 3rd
t	4.4†	8.7†	4.0†	3.4†	3.1†	.40

*Averages and standard deviations of the per cent variation from the individual regression lines drawn from the six determinations for each subject. Thus at high O_2 tensions the first D_{LCO} was on the average 4.4 per cent higher than the second determination and 7.9 per cent higher than the third determination.

†Significant difference.

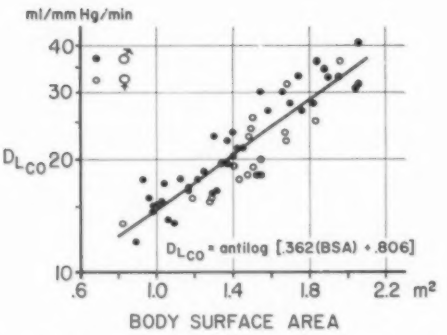


Fig. 2. Lung diffusion (D_{LCO}) vs. body surface area in 59 normal subjects 7 to 40 years of age.

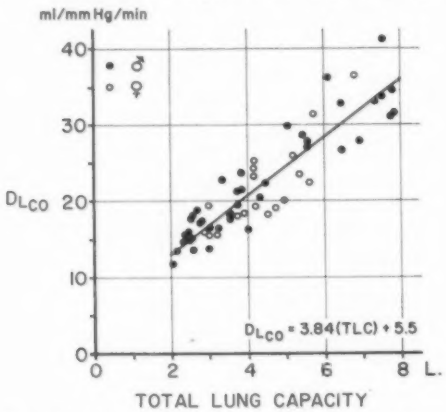


Fig. 3. Lung diffusion (D_{LCO}) vs. total lung capacity in 59 normal subjects 7 to 40 years of age.

ing ventilated alveoli, and θ is a velocity constant related to the oxygen tension inside the capillaries.

Applying this principle, the diffusing capacity of the pulmonary membrane and the pulmonary capillary blood volume were determined in 34 of the subjects. In order to use the formulas described by Roughton and Forster it was necessary to measure D_{LCO} at a high oxygen tension as well as with room air. Consequently three determinations, using a gas mixture of approximately 0.3 per cent carbon monoxide, 10 per cent helium, and 89.7 per cent oxygen, were performed after the subject had taken 6 to 8 deep breaths from the spirometer system which had been filled with 100 per cent oxygen. Since less carbon monoxide is absorbed at high oxygen tensions, the D_{LCO} was determined first at high oxygen concentration. In this way it was felt that back pressure from carbon monoxide–hemoglobin would be minimized.

Gas analyses were done within 1 to 10 minutes after the collection. Approximately 350 ml. was necessary for the analysis which was performed after CO_2 had been removed. A helium catharometer, an infrared CO analyzer, and a paramagnetic O_2 analyzer were connected in series and the sample pulled through by a vibrating membrane vacuum pump. The helium readings were corrected for the N_2 concentrations. The CO_2 concentration measured with an infrared analyzer was found to be consistently between 3 and 5 per cent and hence a standard concentration of 4 per cent was used in order to estimate the concentrating effect of CO_2 removal.

D_{LCO} was calculated according to the Krogh equation[7]* using as alveolar volume the volume of inspired gas mixture plus the residual volume determined by the helium closed-circuit technique. In agreement with the results of others[4] was the finding that residual volume calculated by the helium dilution during the single breath consistently gave too small a value and hence did not provide a satisfactory measurement, presumably because of inadequate mixing.

For the calculations of D_M and V_c the relation proposed by Roughton and Forster[6] and others[8, 9] was used:

$$1/D_{LCO} = 1/D_M + 1/\theta V_c$$

In this equation, $1/D_{LCO}$, $1/D_M$, and $1/\theta V_c$ denote the total resistance of the lungs, the pulmonary membrane, and intracapillary re-

*$D_L = \dfrac{\text{Alveolar volume (STPD)} \times 60}{\text{Time in seconds} \times (\text{barometric pressure} - 47)} \times \log_e \dfrac{\text{Initial CO concentration in the alveolar air}}{\text{Final CO concentration in the expired alveolar sample}}$

D_L is expressed in milliliters CO(STPD) per minute per millimeter of mercury CO tension.

sistance, respectively. The values of $1/\theta$ reported by Roughton and Forster[6] on the basis of an average λ (the ratio of permeability of the red blood cell membrane to the red cell interior) of 2.5 were arbitrarily chosen and $1/\theta$ was plotted versus $1/D_L$. The regression line (Fig. 1) for the sets of points at high and low capillary oxygen tension (P_{CO_2}) could be drawn by eye. D_M and V_c were calculated from the intersection and slope of the regression line respectively and V_c was corrected for the hemoglobin content of the subject's capillary blood with the equation:

$$V_c \text{ (corrected)} = V_c \times 14.9/\text{Hgb. Gm. \%}$$

In arriving at the best value for $1/\theta$, the average pulmonary capillary oxygen tension was estimated by adding 5 mm. to the expired oxygen tension, as suggested by McNeill and co-workers[10]; then the alveolar-capillary gradient was estimated according to the equation: A-c gradient = estimated O_2 consumption/estimated $D_{LCO} \times 1.23$, where D_{LCO} was the diffusion for CO at 120 mm. O_2 tension. The total adjustment of $1/\theta$ usually was small, particularly in the normal subject, so that the estimations produced at worst only a small chance for error (total adjustment from expired alveolar oxygen tension was on the average 2 mm. Hg).

RESULTS

A small significant and progressive decrease in total lung diffusion was found on successive D_{LCO} determinations at both high and low oxygen tensions (Table I). There was no consistent change in alveolar volume or in breath-holding time which might explain this phenomenon. The nonsystematic errors of the method in the measurement of D_{LCO} were calculated as standard deviations from the expected value for each group of determinations (i.e., at high and low alveolar oxygen tensions) (Table I). The results of repeat studies in 2 normal adults and 3 normal children are shown in Table II. (Repeat determinations in one additional patient with congenital heart disease are included in the table.)

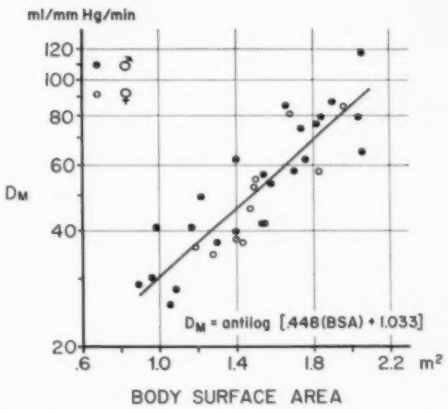


Fig. 4. Membrane diffusion (D_M) vs. body surface area in 34 normal subjects 7 to 40 years of age.

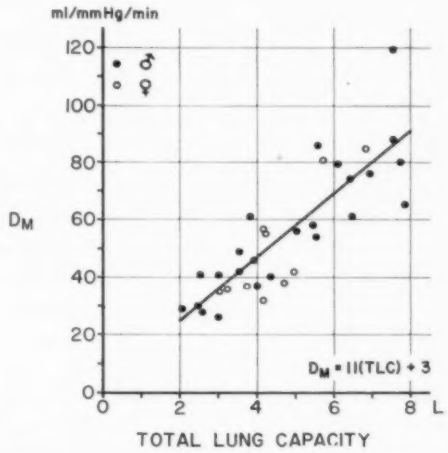


Fig. 5. Membrane diffusion (D_M) vs. total lung capacity in 34 normal subjects 7 to 40 years of age.

The relations between D_{LCO}, D_M, and V_c on the one hand and body surface area and total lung capacity on the other are shown in Tables III and IV and in Figs. 2 to 7.* Ranges have been estimated from the

*The sex, age, height, and weight, together with the D_{LCO}, D_M, and V_c for the individual subjects, may be obtained by requesting Document No. 6584 from the American Documentation Institute, Auxiliary Publications Project, Library of Congress, Washington 25, D. C. (advance payment is required: $1.25 for photoprints or 35 mm. microfilm; make checks or money orders payable to Chief, Photoduplication Service, Library of Congress).

Table II. Repeated determinations of D_{LCO}, D_M, and V_c in 6 subjects

Initials	*Age*	*Diagnosis*	*No. of determinations*	D_{LCO} *(ml./mm. Hg /min.)**	D_M *(ml./mm. Hg /min.)*	V_c *(ml.)*
C. P.	10 9/12	Normal	1	17.5	45	40
			1	17.2	43	39
			1	15.7	32	43
			1	16.3	43	36
			Average	16.7 ± 2.2	40.8 ± 6.9	39.5 ± 3.3
K. J.	13	Normal	1	24.8	79	48
			1	22.7	44	70
			Average	23.8	62	59
C. A.	13 11/12	Normal	1	19.9	37	45
			1	16.4	49	50
			Average	18.2	43	48
B. G.	32	Normal	8	27.9 ± 2.2		
C. D.	40	Normal	10	31.4 ± 2.1		
			1		80	68
			1		71	77
			1		89	74
			Average		80	73
C. J.	26	Atrial septal defect	1	49.1	85	163
			1	45.7	81	146
			1	44.4	75	153
			1	51.4	103	141
			Average	47.7 ± 2.2	86.0 ± 13.8	150.7 ± 12.2

*Each D_{LCO} determination is the average of three single breaths.

graphed data. The regression equations calculated from the data are given in Table V. D_{LCO}, D_M, and V_c are directly related to a measure of lung size such as total lung capacity. No such simple relation is found with surface area, and a semilogarithmic plot has been used in order to construct a more useful graph with straight-line relations. The correlation of D_{LCO}, D_M, and V_c with height and weight was not as good as with surface area and total lung capacity. When body or lung size was taken into account, no differences between the results for males and females were found.

Table III. Values for D_{LCO}, D_M, and V_c predicted on basis of total lung capacity*

TLC (L.)	D_{LCO}† *(ml./mm. Hg/min.)*	D_M *(ml./mm. Hg/min.)*	V_c *(ml.)*
2‡	13(11-16)	25(14-34)	35(26-41)
2.5	15(12-18)	30(18-41)	40(29-47)
3.0	17(13-21)	36(23-48)	44(33-53)
3.5	19(15-24)	42(27-56)	49(37-59)
4.0	21(17-26)	47(32-63)	52(41-66)
4.5	23(18-28)	52(36-70)	58(45-72)
5.0	25(20-30)	58(41-78)	63(49-78)
5.5	27(22-33)	64(45-85)	68(53-85)
6.0	29(24-35)	69(50-92)	72(57-91)
6.5	30(25-37)	75(54-100)	77(61-97)
7.0	32(27-39)	80(59-107)	81(65-104)
7.5	34(29-41)	86(63-114)	86(69-110)
8.0	36(31-44)	92(68-122)	91(73-116)

*Mean values and estimated ranges given.

†D_{LCO} measured at approximately 120 mm. Hg $P_{A_{O_2}}$ tension.

‡Based on extrapolation of regression curve.

The resistance of the membrane ($1/D_M$) was found to account for, on the average, slightly less than half (46 per cent ± 8 per cent) the total lung resistance when room air is breathed. In this study the ratio of resistance of the membrane to intracapillary resistance averaged .81 (S.D., ± .17) and showed a slight but not significant tendency to decrease with increase in body size.

DISCUSSION

Both O_2 and CO have been used for the measurement of lung diffusing capacity, but

Table IV. Values for D_{LCO}, D_M, and V_c predicted on basis of body surface area*

BSA (M.²†)	*D_{LCO}‡ (ml./mm. Hg/min.)*	*D_M (ml./mm. Hg/min.)*	*V_c (ml.)*
.80§	12(10-15)	25(20-36)	32(26-40)
.90§	13(11-17)	27(21-38)	35(28-44)
1.00	15(12-18)	30(23-42)	38(30-48)
1.10	16(13-20)	34(25-46)	41(32-53)
1.20	17(14-21)	38(28-50)	45(34-58)
1.30	19(15-23)	42(31-56)	49(38-64)
1.40	21(16-25)	46(35-62)	53(41-69)
1.50	22(18-27)	51(39-69)	57(45-75)
1.60	24(20-29)	56(43-77)	62(50-81)
1.70	27(22-32)	62(47-85)	68(55-88)
1.80	29(24-35)	69(52-94)	76(60-95)
1.90	31(26-38)	77(57-102)	81(65-101)
2.00	34(29-41)	85(62-111)	87(70-108)
2.10§	37(31-44)	94(67-120)	94(76-114)

*Mean values and estimated ranges given.

†Estimation of surface area based on nomogram from Consolazio and associates.[11]

‡$D_{L_{CO}}$ measured at approximately 120 mm. Hg $P_{A_{O_2}}$ tension.

§Based on extrapolation of regression curve.

Table V. Regression equations and correlation coefficients for D_{LCO}, D_M, and V_c vs. total lung capacity, body surface area, and height*

	Regression equation	*Correlation coefficient*
$D_{L_{CO}}$ (ml./mm. Hg/min.)	= 3.84 (TLC) + 5.5	+.89
	= antilog [.362 (BSA) + .806]	+.91
	= antilog [.656 (Ht) + .308]	+.77
D_M (ml./mm. Hg/min.)	= 11 (TLC) + 3	+.84
	= antilog [.448 (BSA) + 1.033]	+.85
	= antilog [.855 (Ht) + .333]	+.69
V_c (ml.)	= 9.3 (TLC) + 16.5	+.86
	= antilog [.359 (BSA) + 1.220]	+.81
	= antilog [.684 (Ht) + .674]	+.61

*In the equations total lung capacity is expressed in liters, body surface area in square meters, and height in meters.

recently CO has more frequently been employed as the test gas because of ease of analysis and less difficulty with back-pressure corrections. CO has been used both with the steady state of Filley[12] and the single-breath method of Forster.[1] For this present study on both children and adults, the single-breath technique was felt preferable because no measurement of physiologic dead space (ideally necessitating an arterial puncture and blood gas analysis) is involved and variations with changes in alveolar ventilation are eliminated. One of the disadvantages of the single-breath technique is that it requires a greater degree of understanding and cooperation which is impossible for subjects or patients under 5 or 6 years of age. In addition, it is difficult for small children or patients with decreased vital capacity to expire in a single breath a large enough volume to wash out the physiologic dead space and also provide the 350 ml. necessary for the gas analysis.

In considering results of various techniques for the measurement of diffusion, it should be remembered that basic differences account for the different results. Thus, for example, more alveoli are open and more capillaries are exposed to the test gas during the single breath maneuver than during the steady state procedure and this, at least in part, accounts for the greater diffusion measured by the single-breath technique. Variations in the distribution of the test gas and other factors related to the method employed undoubtedly are important but more difficult to evaluate.

The critical evaluation of the methods used in the determination of D_M and V_c is beyond the scope of this report and has been recently considered by others.[6, 13] However, a brief summary of some of the limita-

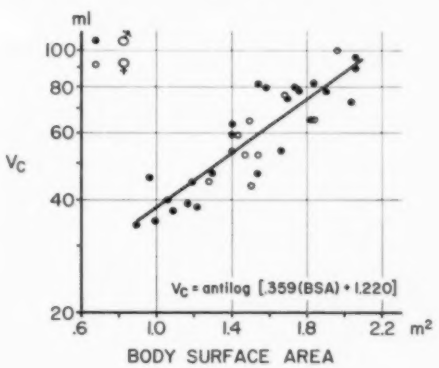


Fig. 6. Pulmonary capillary blood volume (V_c) vs. body surface area in 34 normal subjects 7 to 40 years of age.

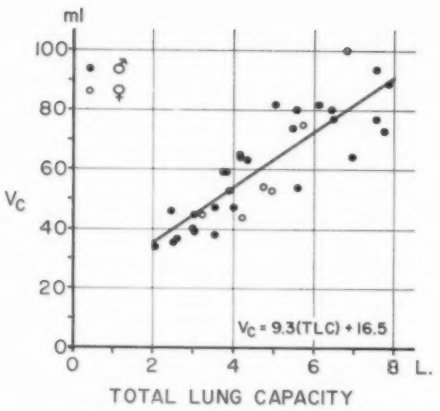


Fig. 7. Pulmonary capillary blood volume (V_c) vs. total lung capacity in 34 normal subjects 7 to 40 years of age.

tions of the technique is necessary for interpretation of the results both in normal subjects and in various pulmonary abnormalities.

The determination of the values for θ at various O_2 tensions has been carried out by Roughton, Forster and co-workers,[6, 14, 15] and the potential errors discussed. Not only are a number of assumptions involved in these determinations, but the final values are based on relatively few studies and may or may not be applicable to all sorts of subjects and patients. In addition θ must be adjusted for the estimated pulmonary capillary blood O_2 tension. Fortunately these limitations are apparently of relatively small significance.

The calculation of pulmonary capillary blood volume depends on the assumption that the measured peripheral capillary and the pulmonary capillary hemoglobin concentrations are the same. No direct comparisons are available but some small error resulting from this assumption is probable.

It has been demonstrated by Forster and co-workers[16] and by Lewis and his associates[17] that progressive accumulation of carbon monoxide–hemoglobin occurs during consecutive tests, producing some decreases in D_{LCO}. In this study, the CO-Hgb concentration was not determined and no correction for this factor was possible. However, calculations show that the maximum amount of CO which may possibly be absorbed during actual tests would account for only a small fraction of the progressive decrease of D_{LCO} observed in the present series (Table I). Since no systematic variations in the performance of the test have been found and since a true progressive change in D_{LCO} or V_c or D_M appears unlikely, this phenomenon is at present unexplained. This error is relatively small and the same progressive change has been found in the biggest group of patients studied (those with heart disease[2]) so the results should be comparable.

The results of other authors using methods similar to ours are shown in Table VI. For purposes of comparison, the values for a person with a surface area of 2 M.^{2} have been tabulated. The present results for D_{LCO} are similar to those of previously reported studies. Regression equations derived from data primarily pertaining to adults are not in agreement with the present formulas (Table V) derived from studies in children, adolescents, and young adults.

No other extensive data are available for single-breath D_{LCO} in normal children. Normal values for steady state D_{LCO} in children have been reported by Strang[20] and Stahlman[21] and correspond to approximately two-thirds of our values; a similar ratio has been found in normal adults.[1, 22]

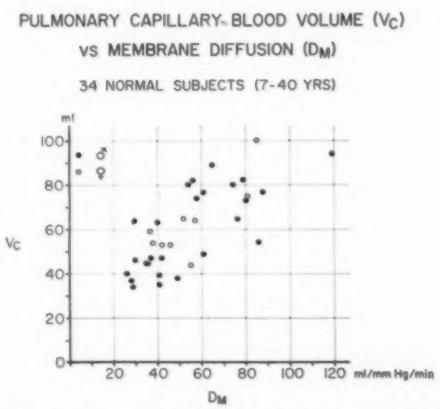


Fig. 8. Pulmonary capillary blood volume (V_c) vs. membrane diffusion (D_M) in 34 normal subjects 7 to 40 years of age.

Table VI. Comparison of reported values for D_{Lco}, D_M, and V_c obtained by breath-holding technique

Authors	*No. of subjects*	*Age (years)*		*Surface area (M^2)*	*D_{Lco} (ml./mm. Hg/min.)*	*D_M (ml./mm. Hg/min.)*	*V_c (ml.)*
		Average	*Range*				
Ogilvie et al.[4]	28	34	8-72	2.00	30.9*		
Ross et al.[18]	8	22	21-24	2.03	34.8 ± 5.9		
McGrath and Thomson[19]	39	40	15-75	2.00	34.0*		
Roughton and Forster[6]	7	Adult		?	30	57	79
McNeill et al.[10]	8	33	23-48	2.01	32.1 ± 2.3	64 ± 12	97 ± 16
Lewis et al.[17]	19	26	21-34	2.00	35.4*	127*	75*
Present series	59	15	7-40	2.00	34.0 ± 6*		
	34	17	7-40	2.00		85 ± 13*	87 ± 10*

*Values predicted for the 2.00 $M.^2$ individual based on regression equation.

The present values for D_M are greater and for V_c are slightly smaller than those reported by McNeill and co-workers.[10] When the present data are compared with those of Lewis and associates[17] our values for D_M are found to be smaller and for V_c greater. The reasons for these differences are not clear, although, as previously mentioned, the unexplained progressive decrease in D_{Lco} may account for some of the discrepancies.

The determinations of D_M have been reproducible and well correlated with body and lung sizes, so that they can apparently be used for comparative purposes. The relation between the resistance of the membrane and the intracapillary resistance found in the present series (.81) is less than that previously reported (1.12) by McNeill and co-workers.[10]

The present data indicate that as the lung grows (at least from the age of 7 years to young adulthood) the pulmonary capillary blood volume and the diffusing capacity of the pulmonary membrane increase in a parallel manner (Fig. 8). It will be of physiologic interest, if the necessary data become available, to see if the parallelism in growth rates also pertains from birth to 7 years.

SUMMARY

Studies of total lung diffusion measured by the single-breath carbon monoxide method have been reported for 59 normal subjects between the ages of 7 and 40 years. In addition determinations of diffusing capacity of the pulmonary membrane and pulmonary capillary blood volume have been performed in 34 of the subjects. A comparison of the present results with those previously reported as well as a brief discussion of some of the limitations of the technique are presented.

REFERENCES

1. Forster, R. E., Cohn, J. E., Briscoe, W. A., Blakemore, W. S., and Riley, R. L.: A Modification of the Krogh Carbon Monoxide Breath Holding Technique for Estimating the Diffusing Capacity of the Lung: A Comparison With Three Other Methods, J. Clin. Invest. **34:** 1417, 1955.
2. Bucci, G., Cook, C. D., and Hamann, J. F.: Studies of Respiratory Physiology in Children. VI. Lung Diffusing Capacity, Pulmonary Capillary Blood Volume and Pulmonary Membrane Resistance in Congenital Heart Disease (to be published).
3. Helliesen, P. J., Cook, C. D., Friedlander, L., and Agathon, S.: Studies of Respiratory Physiology in Children. I. Mechanics of Respiration and Lung Volumes in 85 Normal Children, 5 to 17 Years of Age, Pediatrics **22:** 80, 1958.
4. Ogilvie, C. M., Forster, R. E., Blakemore, W. S., and Morton, J. W.: A Standardized Breath Holding Technique for the Clinical Measurement of the Diffusing Capacity of the Lung for Carbon Monoxide, J. Clin. Invest. **36:** 1, 1957.
5. Roughton, F. J. W.: The Average Time Spent by the Blood in the Human Lung Capillary and Its Relation to the Rates of CO Uptake and Elimination in Man, Am. J. Physiol. **143:** 621, 1945.
6. Roughton, F. J. W., and Forster, R. E.: Relative Importance of Diffusion and Chemical Reaction Rates in Determining Rate of Exchange of Gases in the Human Lung, With Special Reference to True Diffusing

Capacity of Pulmonary Membrane and Volume of Blood in the Lung Capillaries, J. Appl. Physiol. **11:** 290, 1957.
7. Krogh, M.: The Diffusion of Gases Through the Lungs of Man, J. Physiol. **49:** 271, 1914.
8. Kruhoffer, P.: Lung Diffusion Coefficient for CO in Normal Human Subjects by Means of $C^{14}O$, Acta physiol. scandinav. **32:** 106, 1954.
9. Gibson, Q. H., Kreuzer, F., Meda, E., and Roughton, F. J. W.: Kinetics of Human Haemoglobin in Solution and in Red Cells at 37° C., J. Physiol. **129:** 65, 1955.
10. McNeill, R. S., Rankin, J., and Forster, R. E.: The Diffusing Capacity of the Pulmonary Membrane and the Pulmonary Capillary Blood Volume in Cardiopulmonary Disease, Clin. Sc. **17:** 465, 1958.
11. Consolazio, C. F., Johnson, R. E., and Marek, E.: Metabolic Methods, St. Louis, 1951, The C. V. Mosby Company, p. 338.
12. Filley, G. F., MacIntosh, D. J., and Wright, G. W.: CO Uptake and Pulmonary Diffusing Capacity in Normal Subjects at Rest and During Exercise, J. Clin. Invest. **33:** 530, 1954.
13. Forster, R. E.: Exchange of Gases Between Alveolar Air and Pulmonary Capillary Blood: Pulmonary Diffusing Capacity, Physiol. Rev. **37:** 391, 1957.
14. Forster, R. E., Roughton, F. J. W., Kreuzer, F., and Briscoe, W. A.: Photocolorimetric Determination of Rate of Uptake of CO and O_2 by Reduced Human Red Cell Suspensions at 37° C., J. Appl. Physiol. **11:** 260, 1957.
15. Roughton, F. J. W., Forster, R. E., and Cander, L.: Rate at Which Carbon Monoxide Replaces Oxygen From Combination With Human Hemoglobin in Solution and in the Red Cell, J. Appl. Physiol. **11:** 269, 1957.
16. Forster, R. E., Fowler, W. S., Bates, D. V., and Van Lingen, B.: The Absorption of Carbon Monoxide by the Lungs During Breath Holding, J. Clin. Invest. **33:** 1135, 1954.
17. Lewis, B. M., Lin, T. H., Noe, F. E., and Komisaruk, R.: The Measurement of Pulmonary Capillary Blood Volume and Pulmonary Membrane Diffusing Capacity in Normal Subjects: the Effect of Exercise and Position, J. Clin. Invest. **37:** 1061, 1958.
18. Ross, J. C., Frayser, R., and Hickam, J. B.: A Study of the Mechanism by Which Exercise Increases the Pulmonary Diffusing Capacity for Carbon Monoxide, J. Clin. Invest. **38:** 916, 1959.
19. McGrath, M. W., and Thomson, M. L.: The Effect of Age, Body Size and Lung Volume Change on Alveolar-Capillary Permeability and Diffusing Capacity in Man, J. Physiol. **146:** 572, 1959.
20. Strang, L. B.: Measurements of Pulmonary Diffusing Capacity in Children, Arch. Dis. Childhood **35:** 232, 1960.
21. Stahlman, M.: The Use of Carbon Monoxide Diffusion Capacity in the Evaluation of Pulmonary Function in Infants and Children (abstract), A. M. A. J. Dis. Child. **100:** 527, 1960.
22. Marks, A., Cugell, D. W., Cadigan, J. B., and Gaensler, E. A.: Clinical Determinations of the Diffusion Capacity of the Lungs. Comparison of Methods in Normal Subjects and Patients With Alveolar-Capillary Block Syndrome, Am. J. Med. **22:** 51, 1957.

The role of lysolecithin and cholesterol in icterus neonatorum

A. Gotlieb, M.D.,* J. Pesach, and A. Rimon, Ph.D.

TEL-AVIV, ISRAEL

ICTERUS NEONATORUM is a phenomenon known for many generations. Many theories have been advanced to explain its symptomatology; the outstanding are: (1) the hemolytic theory of Goldbloom and Gottlieb,[1-2] and (2) the theory of immaturity of the liver, suggested by Billing and colleagues.[3-4] The former explains the formation of icterus neonatorum on the basis of increased hemolysis of the newborn's erythrocytes. This is further supported by Bercovici, Welish, and Nelken,[5] who were able to demonstrate the presence of a lytic substance in the serum of the cord blood. The latter theory attributes icterus neonatorum to the immaturity of the liver. Lathe and Walker[6] and Dutton[7] found that the action of the enzymatic system responsible for the conjugation of bilirubin is markedly impaired in the liver of the newborn. The levels of the glucuronyl transferase and of uridine diphosphate glucose dehydrogenase (UDPG dehydrogenase) were very low or not measurable in the fetus and in the newborn. This is apparently one of the causes for the relative increase of indirect bilirubin in these cases.

It seemed to us each theory in itself was insufficient to explain the pathogenesis of neonatal jaundice.

While studying cholesterol levels in cord blood and sera of newborn infants in the first few days of life, we were impressed by the considerable increase in cholesterol (especially in its free form) in the sera of intensely jaundiced infants. Considering the fact that erythrocytes contain cholesterol mostly in its free form, we decided to search for a possible natural substance which could explain the phenomenon of hemolysis and the liberation of free cholesterol from the erythrocytes.

Blood phosphatides have the capacity of forming lytic products while under the influence of specific enzymes; lysolecithin is frequently formed in nature and responsible for hemolysis (scorpions, some snake venom, etc.). Lecithin makes up about two thirds of blood phospholipids.

These facts directed our attention to lysolecithin as a likely hemolytic factor in icterus neonatorum.

The work of Bercovici and associates, in which they demonstrated the increase in hemolytic activity of cord blood sera after

From the Government Hospital, Jaffa, and the Marcus Memorial Blood Institute, Jaffa, Magen David Adom in Israel.

**Address, Head, Pediatric Department A, 31 Pinsker Street, Tel-Aviv, Israel.*

incubation and heating was an additional encouragement to follow this line of investigation.

MATERIALS AND METHODS

Two groups of newborn infants delivered in the Government Hospital were studied. The first consisted of 18 infants with icterus neonatorum; the second group, of 10 infants without icterus. In the nonicteric group we included newborn infants with no clinical signs of jaundice whose bilirubin level on the fourth day of life was lower than 3 mg. per 100 ml. The fourth day was chosen for the blood examination because many authors state, and our own observation supports it, that icterus neonatorum reaches its peak on the third or fourth day of life. The infants of the icteric group showed signs of clinical jaundice ranging from just a yellow tinge to marked discoloration.

Cord blood was collected in sterile test tubes. On the fourth day of life, blood was again taken from the jugular vein or the frontal sinus. In each instance the tubes were kept in the refrigerator until examined (not over a few hours). The tubes were then centrifuged and the serum was separated and analysed.

Cholesterol and cholesterol ester were determined by the method of Sackett.[8]

Bilirubin was determined from the same serum by the method of Malloy-Evelyn.[9]

The ability of a serum to produce lysolecithin was investigated by chromatography of the serum extract after incubation with lecithin. Three milliliters of a suspension containing 15 micromols of lecithin and 0.05 ml. of a 0.4 M solution of calcium chloride ($CaCl^2$) were added to 1 ml. of serum and incubated overnight at 37° C. After incubation, the reaction was stopped by the addition of 10 ml. of 20 per cent methanol in chloroform. The extraction of lipids was carried out by heating the methanol-chloroform-serum mixture in a bath of boiling water for a few minutes and centrifuging. The precipitate (serum proteins) was resuspended in 20 per cent methanol-chloroform and again centrifuged. The combined

Table I. Newborn infants with icterus neonatorum

Case No.	Cord blood					Fourth day blood				
	Lysolecithin	Cholesterol (mg. %)			Bilirubin (mg. %)	Lysolecithin	Cholesterol (mg. %)			Bilirubin (mg. %)
		Free	Ester	Total			Free	Ester	Total	
1	+	35	41	76	2.08	+	81	43	124	5.60
2	+	35	46	81	2.08	+	100	57	157	11.50
3	+	30	29	59	1.28	+	88	78	166	5.28
4	+	11	35	46	1.13	+	60	32	92	5.90
5	+	17	33	50	0.96	+	60	51	111	3.90
6	+	28	50	78	0.96	+	80	47	127	7.05
7	+	19	28	47	1.64	+	53	25	78	7.20
8	+	36	33	69	1.65	+	67	33	100	7.40
9	+	36	33	69	1.46	+	78	58	136	7.20
10	+	22	42	64	1.45	+	88	56	144	6.60
11	+	39	39	78	1.42	+	83	39	122	4.80
12	+	39	47	86	1.27	+	83	67	150	8.20
13	+	27	42	69	1.80	+	54	44	98	6.40
14	-	28	44	72	0.96	-	80	103	183	6.97
15	+	24	56	80	2.14	+	94	67	161	8.70
16	+	32	40	72	1.33	+	87	43	130	7.50
17	-	20	44	64	1.25	-	66	55	121	8.60
18	+	28	36	64	1.33	+	66	61	127	7.05
Mean		28.1	39.9	68	1.45		76	53.3	129.3	6.99
S.D.	±	7.9	7.3	11.7	0.14		12.9	17.8	26.4	1.7

Mean cholesterol free ester ratio in cord blood = 0.70.
Mean cholesterol free ester ratio in fourth-day blood = 1.42.

Table II. Newborn infants without icterus neonatorum

Case No.	*Cord blood*					*Fourth day blood*				
	Lyso-lecithin	*Cholesterol (mg. %)*			*Bilirubin (mg. %)*	*Lyso-lecithin*	*Cholesterol (mg. %)*			*Bilirubin (mg. %)*
		Free	*Ester*	*Total*			*Free*	*Ester*	*Total*	
1	-	30	39	69	1.24	-	39	83	122	0.98
2	-	36	56	92	1.15	-	50	58	108	1.48
3	-	14	69	83	1.15	-	47	70	117	1.80
4	-	32	38	70	0.56	-	35	57	92	2.04
5	-	19	51	70	1.12	-	35	59	94	1.44
6	-	32	22	54	0.96	-	54	43	97	1.76
7	-	33	27	60	0.81	-	43	42	85	1.25
8	-	38	42	80	1.18	-	58	72	130	2.64
9	-	28	39	67	1.41	-	38	45	83	2.96
10	+	36	39	75	1.41	+	68	42	110	2.65
Mean		29.8	42.2	72	1.09		46.7	57.1	103.8	1.90
S.D.	±	7.7	13.7	11.1	0.26		9.2	14.4	16.9	0.66

Mean cholesterol free ester ratio cord blood = 0.70.
Mean cholesterol free ester ratio fourth-day blood = 0.80.

supernatants from the first and second extractions were evaporated to dryness in a rotating vacuum evaporator. The lipids were redissolved in minimal amounts of 20 per cent methanol-chloroform and applied to the chromatograms. Chromatography was performed following the method of Lea and associates[10] by the descending technique on silica-impregnated paper with the use of 20 per cent (v/v) methanol-chloroform as a solvent at room temperature (26° C.). Whatman No. 1 filter paper was cut into 28 by 23 cm. sheets. These were impregnated by immersion in sodium silicate solution (commercial water glass diluted with an equal volume of water) for about 1 minute; drained and transferred into 6 N-hydrochloric acid solution for 30 minutes. The papers were then washed several times with distilled water and dried at room temperature. Drops of serum extract were applied to the starting line of the chromatogram and the paper inserted into a 30 by 18 by 56 cm. jar for chromatography. After development (5 to 6 hours) the chromatograms were dried at room temperature for 30 minutes and then immersed for 2 minutes in a 0.001 per cent solution of rhodamine 6 G.[11] The excess of the reagent was washed with water and the lipid spots observed under ultraviolet light.

The hemolytic effect of lysolecithin was determined by the increase of the hemoglobin concentration measured colorimetrically in solutions of 5 ml. saline, 1 ml. of 2 per cent erythrocyte suspension (in saline), and varied quantities of lysolecithin.

Hemolysis in the presence of cholesterol was determined as above, except that 5 ml. of cholesterol containing saline (100 mg. per cent) was added instead of 5 ml. of saline alone. After 15 minutes of incubation at 37° C. the mixture was centrifuged for 5 minutes and the supernatant measured in a Beckman Model C colorimeter (green filter). The results were expressed as a percentage of total hemolysis, produced by the addition of 1 ml. of the 2 per cent erythrocytes suspension to 5 ml. of distilled water.

Lecithin was prepared from egg yolk according to the method described by Hanahan and colleagues[12] by fractionation on an alumina column. Lecithin obtained by this method contained traces of lysolecithin. However, in the concentrations used in this work the lysolecithin was so highly diluted as to be undetectable.

Lysolecithin was prepared from egg lecithin by the method of Hanahan.[13]

RESULTS

In the icteric group there was a significant increase in serum bilirubin level on the

fourth day of life, as compared to that of the cord blood. This increase was accompanied, generally, by a rise in serum cholesterol, especially the free form (Table I). The mean ratio of free cholesterol to cholesterol ester increased considerably during the first 4 days of life from 0.70 to 1.42. The presence of lysolecithin was demonstrated in 16 of the 18 icteric infants.

In the nonicteric cases (Table II) there was only a slight increase in bilirubin (0.8 mg. per cent) as well as in cholesterol levels. The ratio of free cholesterol to cholesterol ester remained practically unchanged. Lysolecithin was demonstrated in only 1 of 10 infants studied. In addition, sera from 12 adults and 8 infants aged 1 to 3 months were studied in a similar way and no lysolecithin was demonstrated.

Fig. 1 shows one of the chromatograms which is quite typical. It can be seen that lysolecithin was formed after incubation of cord blood with lecithin *(E)*. Cord blood serum without incubation *(D)* or adult serum with *(C)* and without *(B)* incubation did not show the typical spot for lysolecithin. Fourth-day blood serum always gave the same results as cord blood in the same infant.

Fig. 2 represents the effect of the presence of 100 mg. per cent of cholesterol on the hemolytic action of varying concentrations of lysolecithin. It is quite apparent that the cholesterol inhibits the hemolytic effect of lysolecithin. Thus, for instance, the hemolysis caused by 25 μg of lysolecithin was 22 per cent in the presence of cholesterol, compared to 64 per cent of hemolysis obtained by the same amount of lysolecithin in the absence of cholesterol.

DISCUSSION

The theory that icterus neonatorum is due to hemolysis has been sponsored by many authors.[1-2] This is based on the facts that the number of erythrocytes[1-4] and amount of hemoglobin decrease and that indirect serum bilirubin rises in the first few days of life.

In the present studies we could demonstrate the formation of lysolecithin from

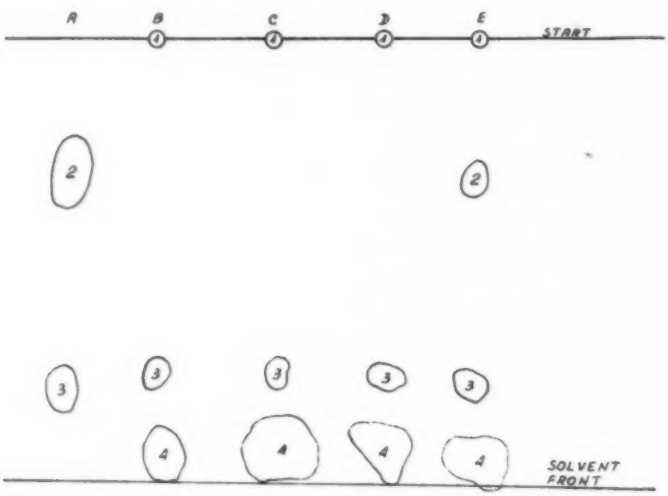


Fig. 1. A typical chromatogram. *A*, Mixture of lecithin and lysolecithin. *B*, Normal adult serum without incubation. *C*, Normal adult serum after incubation. *D*, Cord blood serum before incubation. *E*, Cord blood serum after incubation. *1*, May represent traces of sphingomyelin. *2*, Corresponds to lysolecithin. *3*, Corresponds to lecithin. *4*, Probably neutral lipids and fatty acids.

lecithin in the presence of sera of cord blood or fourth-day blood of infants with neonatal jaundice. As lysolecithin is a well-known hemolytic substance, we believe it is the responsible factor for hemolysis of the newborn. In the infants without icterus neonatorum no lysolecithin could be demonstrated in 9 of 10 cases.

Bercovici and co-workers[5] demonstrated that 68 of 101 cord sera possessed ability to lyse papainized red blood cells of adults. However, they did not state whether any or how many of these infants developed icterus neonatorum. Heating of the cord sera at 56° C. for 30 minutes enhanced the lytic activity or revealed hemolytic properties in some specimens that were previously negative. They theorized that a heat-labile factor in the serum might protect the papainized erythrocytes. In the light of our findings, this observation may be explained on the basis of increased lysolecithin in the heated sera, since lecithinase A is known to be a thermostable enzyme.

We do admit that the immaturity of the liver also plays an important role in this process.[5-6] We would therefore suggest that both hemolysis and liver immaturity are involved in icterus neonatorum.

When Table I and Table II are compared, no significant differences are apparent between the mean cholesterol levels in the cord blood sera of both groups. A much greater alteration in the levels and especially in the ratio between free and esterified cholesterol appears on the fourth day between the two groups of infants.

There are two possible explanations for the great rise in cholesterol (especially the free form) in the icteric group. It may be exogenous (i.e., alimentary) or endogenous.

It is unlikely that this rise in cholesterol is of alimentary origin. During the first 24 hours of life our infants are not fed at all; in the second 24 hours they are breast-fed, receiving generally from 0 to 10 Gm. 5 to 6 times daily; on the third day the amount of colostrum which they receive increases from 10 to 20 Gm. per feeding to 30 to 50 Gm. on the fourth day (all infants are weighed before and after feedings). Blood was taken on the fourth day in the morning before feeding. The amount of colostrum ingested is too small in our opinion to account for such a rise in cholesterol.

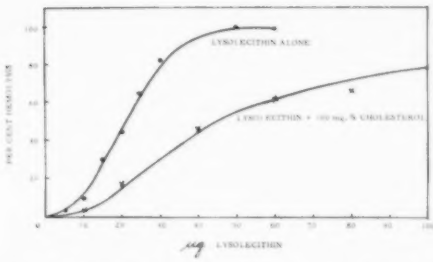


Fig. 2. The effect of cholesterol on the hemolytic potency of lysolecithin.

Colostrum in addition contains a much lower quantity of lipids as compared with normal maternal milk, which on the fourth day after delivery does not yet exist. Thus, in spite of the fact that both groups received a similar low-cholesterol diet, there was a marked difference in cholesterol levels. For the reasons stated above, we assume an endogenous source for the marked rise in cholesterol, mostly in the free form, in the icteric group. A possible cause for the greater rise in cholesterol as well as in the indirect bilirubin in the icteric group may be hemolysis. It is known that erythrocytes contain 89 mg. per cent of free cholesterol[15] and only 29 mg. per cent of esterified cholesterol. Through the hemolysis of erythrocytes the cholesterol, mostly in the free form, is liberated into the blood stream and raises the level of this substance as well as of indirect bilirubin which cannot be properly handled by the immature liver.

The liver immaturity probably accounts for the fact that there is no constant correlation between blood cholesterol and indirect bilirubin values. If hemolysis were the only factor in icterus neonatorum, such a relationship would be expected.

If we accept the existence of hemolysis in icterus neonatorum and that it is probably due to the potent hemolytic substance lysolecithin, we might go a step further. Choles-

terol exerts an inhibitory effect on the hemolytic action of lysolecithin[16] (Fig. 2). When hemolysis takes place and erythrocytes are destroyed, the cholesterol thus liberated into the blood stream may therefore inhibit the hemolytic action of lysolecithin, making icterus neonatorum a self-limited phenomenon.

Other authors[11] found lysolecithin in normal adult serum, but we were unable to confirm their results in sera of adults and in those of infants aged 1 to 3 months. This is possibly due to our technique, in which the small amounts of lysolecithin present normally in adult serum are diluted beyond the possibility of detection.

Our experimental data point to the formation of lysolecithin in sera of infants with neonatal jaundice, but do not prove how it is formed. This may be either by the action of lecithinase A in the icteric infant's blood which is perhaps absent in adult blood; or by the action in adult blood of lecithinase A and a potent lysolecithinase (lecithinase B), the latter being absent from the icteric infant's blood. This problem is at present under investigation. We did not determine the natural substrate of lecithinase A in vivo; this may be lecithin, cephalin, or any other phosphatide, as it is known that each one of them may form a lytic product under the influence of lecithinase A. This problem is also now under investigation.

SUMMARY

Two groups of newborn infants were studied, one with icterus neonatorum and one without. Cord blood serum and fourth-day blood serum were examined for free and esterified cholesterol, bilirubin (which was always indirect), and enzymatic formation of lysolecithin. There was a marked rise in free cholesterol and bilirubin in the fourth-day blood sera of the icteric group, compared with those of the infants in the nonicteric group. Formation of lysolecithin, a strong hemolytic substance, was demonstrated in 16 of 18 cases of the icteric group and in only 1 of 10 nonicteric infants.

It is suggested that icterus neonatorum is caused by a combination of two factors: (1) hemolysis and (2) immaturity of the liver, each factor complementing the other. The enzymatic formation of lysolecithin is suggested as a causative factor of the hemolysis. An inhibitory effect of cholesterol on the hemolytic action of lysolecithin was demonstrated. The hemolytic process is probably self-controlled by the action of cholesterol, liberated from the destroyed erythrocytes.

We wish to express our gratitude to Drs. D. Beckner, A. Gefel, J. Glazer, B. Kounine, and J. Rikover for their help and advice. We are grateful to G. Zann, R.N., and her staff of the Delivery Room, and to R. Bracha, R.N., and her staff of the Nursery Unit for their assistance and collaboration in collecting the blood samples.

REFERENCES

1. Goldbloom, A., and Gottlieb, R.: Icterus Neonatorum, Am. J. Dis. Child. **38:** 57, 1929.
2. Amberg, S., and Logan, G. B.: In Brennemann's Practice of Pediatrics, Hagerstown, Md., 1959, W. F. Prior Company, vol. 3, chap. 11, p. 21.
3. Billing, B., Cole, P. G., and Lathe, G. H.: Increased Plasma Bilirubin in Newborn in Relation to Birth Weight, Brit. M. J. **2:** 1263, 1954.
4. Billing, B., and Lathe, G. H.: The Excretion of Bilirubin as an Ester Glucuronide Giving the Direct van den Bergh Reaction, Biochem. J. **63:** 6, 1956.
5. Bercovici, B., Welish, G., and Nelken, D.: Lytic Property of Cord Blood Serum, Proc. Soc. Exper. Biol. & Med. **100:** 846, 1959.
6. Lathe, G. H., and Walker, M.: An Enzyme Defect in Human Neonatal Jaundice and in Gunn Strain of Jaundice Rats, Biochem. J. **67:** 9, 1957.
7. Dutton, G. J.: Glucuronide Synthesis in Foetal Liver and Kidney, Lancet **1:** 49, 1958.
8. Sackett, G. E.: Modification of Bloor Method for the Determination in Whole Blood or Blood Serum, J. Biol. Chem. **64:** 203, 1939.
9. Malloy, H. T., and Evelyn, K. A.: Determination of Bilirubin With Photoelectric Colorimeter, J. Biol. Chem. **119:** 481, 1937.
10. Lea, C. H., Rhodes, D. N., and Stoll, R. D.: Phospholipids; 3. On the Chromatographic Separation of Glycerophospholipids, Biochem. J. **60:** 353, 1955.
11. Marinetti, G. V., Albrecht, M., Ford, T., and Stotz, E.: Analysis of Human Plasma Phosphatides by Paper Chromatography, Biochem. et biophys. acta **36:** 4, 1959.

12. Hanahan, D. J., Turner, M. B., and Jyko, M. E.: The Isolation of Egg Phosphatidyl-Choline by an Absorption Column Technique, J. Biol. Chem. **192:** 623, 1951.
13. Hanahan, D. J.: A Convenient Route to Distearoyl-L-X and B-Mono-Stearoyllecithin, J. Biol. Chem. **211:** 321, 1954.
14. Sanford, H. N.: In Brennemann's Practice of Pediatrics, Hagerstown, Md., 1959, W. F. Prior Company, vol. 3, chap. 15, pp. 2-3.
15. Kugelmann, I. N.: Biochemistry of Blood in Health and Disease, Springfield, Ill., 1959, Charles C Thomas, Publisher, p. 303.
16. Ponder, E.: Hemolysis and Related Phenomena, New York, 1948, Grune & Stratton, Inc., p. 269.

Toxoplasma from the eggs of the domestic fowl (Gallus gallus)

Abstract. Toxoplasmata of varying grades of virulence have been isolated from eggs laid by clinically asymptomatic hens and from their internal organs. The strains so recovered were identified as Toxoplasmata gondii by morphological, serological, cultural, and pathogenic criteria. These findings strongly suggest that toxoplasmosis may be contracted through the eating of raw or undercooked infected eggs.

P. G. Pande, R. R. Shukla, and P. C. Sekariah
(From Science, vol. 133, no. 3453, March 3, 1961, p. 648.)

Growth and development of children with galactosemia

George N. Donnell, M.D., Manuel Collado, M.D., and Richard Koch, M.D.*

LOS ANGELES, CALIF.

CLARIFICATION of the biochemical basis of galactosemia[1-5] and the availability of enzymatic methods to assist in clinical evaluation has given impetus to the study of this disorder.[6] Children with galactosemia are now being found in sufficient number to make various definitive studies possible. As one consequence, the genetic aspects of the disease have been elucidated.[7, 8] Longitudinal studies of growth and development in galactosemic children, necessarily infrequent in the past,[9-11] are now possible.

Sixteen families with 24 affected children have been studied at the Childrens Hospital of Los Angeles in the past 12 years. Sixteen are living. Eight died in early infancy with findings strongly suggestive of galactosemia. Longitudinal observations have been made of mental and physical development in 15 of the children. The other is in an institution for the mentally retarded. The purpose of this report is to present observations on the growth and development of these children and to present data on the effects of dietary management in relation to the attainment and maintenance of optimal intellectual capacity.

From the Metabolic Research Laboratories and the Child Development Clinic of the Childrens Hospital, Los Angeles, and the Department of Pediatrics of the University of Southern California School of Medicine, Los Angeles, California. *The Child Development Clinic is partially supported by a grant from the Children's Bureau, Department of Health, Education, and Welfare, Washington, D. C.*

Children's Hospital Society of Los Angeles, 4614 Sunset Boulevard, Los Angeles 27, Calif.

METHODS AND MATERIALS

Galactose intolerance and the absence of galactose-1-phosphate-uridyl transferase in erythrocytes were demonstrated in all 16 living children with galactosemia.* Galactose tolerance tests and enzymatic assay of galactose-1-phosphate-uridyl transferase were performed by methods previously described.[7, 8, 12] Physical and psychological measurements were performed in a uniform manner. In children 2 years of age or less, height was measured in the recumbent position. In the older group, height was measured in the erect posture. Height and weight were plotted on the Standard University of Iowa growth charts. In addition, skeletal maturation was assessed by comparison with norms in the atlas of Greulich and Pyle. Children less than 4 years of age were tested by Gesell Developmental Scales at regular intervals by the same examiner (R. K.). The appropriate

*We are indebted to the Dixon State Hospital in Illinois for their generous help in supplying the serum samples and psychometric data concerning the institutionalized case.

Wechsler Scales of Intelligence were administered in older children and adults by a clinical psychologist. For the purpose of this study, only single intelligence tests were performed on parents and unaffected siblings. Developmental progress of children with galactosemia was evaluated periodically, however.*

CLINICAL RESULTS

This report comprises observations on 7 female and 8 male children with galactosemia (Table I). The period of observation ranged from 18 months to 12 years with a mean of 5 years, 9 months.

Twelve were given Nutramigen as the basic diet during infancy. Three of the children were fed soya bean formula for varying periods. With increasing age appropriate solid foods were added. Parents were instructed to avoid carefully foods containing dairy products.

The birth weight of the galactosemic children varied from 4 pounds, 7 ounces, to 10 pounds, 2 ounces, averaging 7 pounds. Only one infant was premature (Case 9). In a review of the literature, only one of 70 birth weights recorded for galactosemic children was in the range of prematurity. The relative scarcity of recorded cases affecting premature infants may reflect difficulty in diagnosis rather than an attribute of the disease. Certain clinical signs of galactosemia resemble conditions commonly encountered in premature infants, such as jaundice, feeding difficulties, and sepsis.

Observations recorded during the first year of life are shown in Fig. 1. Figs. 2 and 3 illustrate measurements of growth in the older children. During infancy, nearly all deviated significantly from the mean (Fig. 1). Physical growth thereafter was satisfactory in 14 and in keeping with patterns of growth of unaffected siblings and other members of the family. The disease was diagnosed in the only child with significantly retarded growth (Case 8) at 15 months of age and her dietary management was unsatisfactory.

The intelligence quotients of parents, siblings, and other galactosemic children are shown in Fig. 4. Quotients of the parents ranged from 85 to 123, average 107 and median 108. Quotients of siblings ranged from 30 to 119, average 94 and median 94. In contrast, those of the galactosemic children varied from 11 to 108, average only 79 and median 84. Four of these are mentally defective, 6 borderline, and 6 low normal to normal in intelligence. One of the mentally defective subjects is the untreated sibling in the state institution who has an estimated intelligence quotient of 11.

Our data suggest that very early diagnosis followed by immediate institution of treatment permits more satisfactory mental development. In Fig. 5 this relationship is illustrated by comparison of the age at the time treatment was begun with the most recent estimate of mental development. For this purpose we have considered Developmental Quotient (D.Q.) equal to Intelligence Quotient (I.Q.).

Ten children were found to have cataracts at the time of diagnosis. Improvement followed elimination of galactose from the diet, but complete regression did not occur.[13] Only Patients 1 and 2 suffered sufficient impairment of vision to require attendance at a school for visually handicapped children. The diagnosis was established in these 2 children at 5 and 14 months of age, respectively, and they were the first in the present series of patients. Case 8 may yet need to attend a school for visually handicapped children because of the state of her cataracts. Convulsions due to hypoglycemia[14] have not been observed.

Except for electroencephalographic abnormalities, none of the 15 children under our surveillance have shown specific neurological

*In view of the unsettled controversy concerning the reliability of Development Quotient scores obtained from Gesell Scales and their validity when compared with the Intelligence Quotient measurements of such instruments as Stanford-Binet Scales or WISC, we chose to make periodic estimates of Developmental Quotients in the galactosemic children. Thus, each subject served as his own control, and the series of measurements increased the reliability of the over-all estimate.

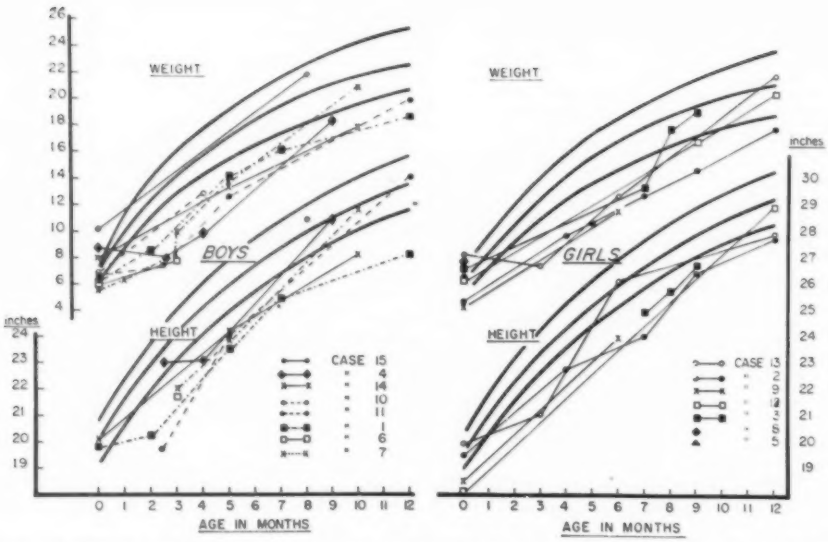


Fig. 1. Weight and height measurements obtained during the first 12 months of life in 15 galactosemic children.

abnormalities. Electroencephalograms were performed on 14 subjects; 5 were abnormal. Four were diffusely abnormal and the other revealed a spike-wave focus in the right occipital area. Four of the normal electroencephalograms were performed concurrently with standard galactose tolerance tests and the patterns were not influenced by galactose loading.[15] Electroencephalographic abnormalities could not be correlated with the intellectual capacity of individual children.

Skeletal age was retarded in 8 (Fig. 6) without apparent relation to age at time of diagnosis, diet, or intelligence. Protein-bound iodine was measured and did not differ from the normal level.

DISCUSSION

Few detailed studies of the growth and development of galactosemic children have been recorded.[9-11] Present evidence suggests that exclusion of galactose from the diet can prevent and even reverse many clinical features of the disease, but substantiating long-term evaluation of physical and mental development has not been available in treated children.

The data reported herein show that dietary restriction of galactose permits a child with galactosemia to achieve a pattern of growth comparing favorably in both height and weight with that of normal children. The growth curves (Figs. 1, 2, 3) show that rapid gains in weight occur very soon after inauguration of treatment and that accepted norms are usually reached in 8 to 12 months. Only 3 children, all female, were as much as one standard deviation below the norm in weight during the first 2 years of life. Prematurity and the fact that she was partially reared on a soya bean formula might have contributed to the slow growth of Case 9. In the other 2 (Cases 2 and 8) diagnosis was made rather late, the first at 5 months and the other at 15 months of age. Case 2 adhered to her diet rigidly for 6 years, but minor dietary violations have occurred during the past few years. In Case 8 the diagnosis was made at 15 months of age, at which time she was severely mentally retarded and exhibited bilateral cataracts and hepatomegaly. She was unable to roll over, sit, or stand. After 9 months on a diet of Nutramigen she had improved markedly

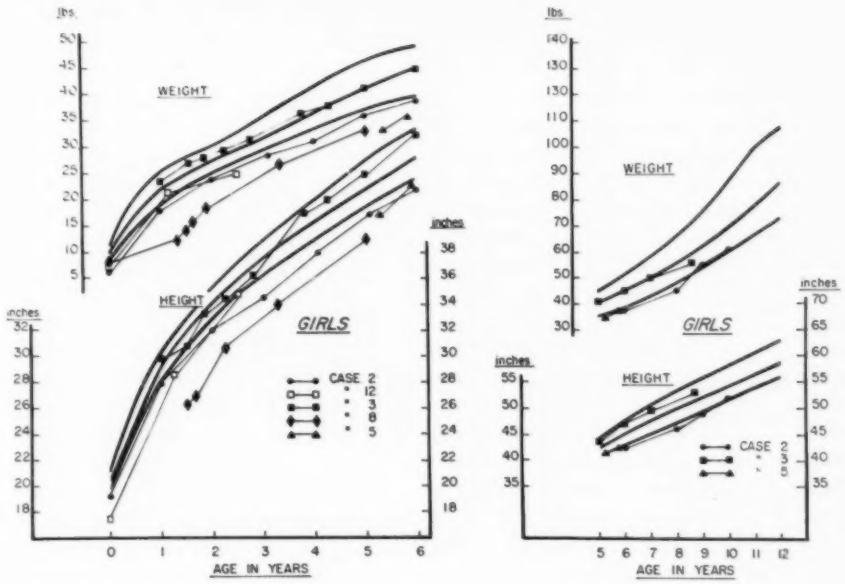


Fig. 2. Weight and height measurements in female galactosemic children.

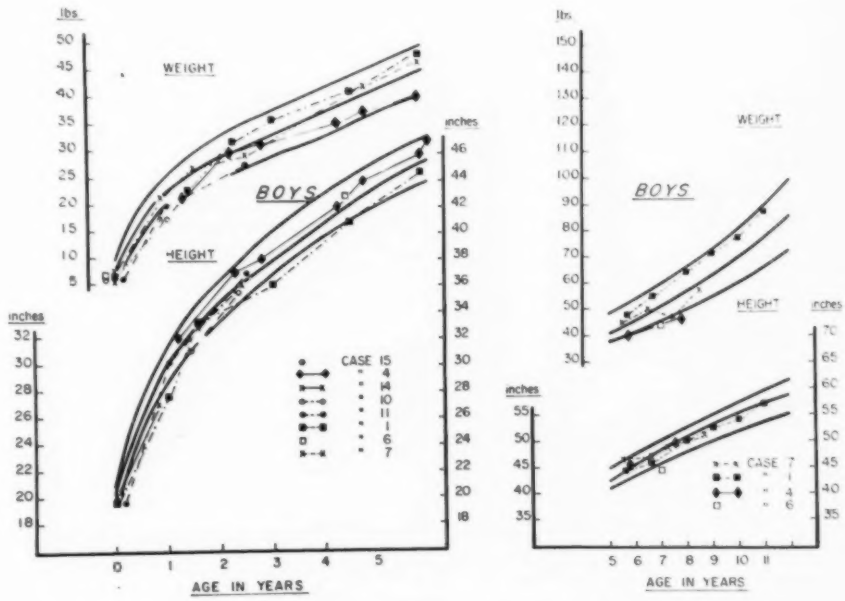


Fig. 3. Weight and height measurements in male galactosemic children.

and learned to walk and say a few words. She was then lost to follow-up for 2 years, during which period little attention had been paid to her diet. She was receiving an average of one glass of milk per day and free intake of other galactose-containing foods as well. Her I.Q. at 5 years of age had dropped to 25. Failure to exclude dietary galactose is reflected in her poor developmental progress. In effect, the circumstances of these exceptions reinforce the general conclusions to be drawn from the growth curves.

The effect of diet on mental development is less certain, and the data reported are insufficient for any firm conclusion. An extensive search disclosed only 61 statements about the intelligence of galactosemic children. Thirty-three were said to be normal and 28 mentally retarded. Psychometric scores were recorded for only 15 children, ranging from 37 to 100. Only Townsend,[9] Holzel,[10] and Bernheim[11] have presented longitudinal data. No correlations could be made from their data between dietary management and intellectual development.

It is important to determine whether mental retardation is part of the genetic defect or a consequence of its metabolic manifestations. No evidence is presently available in support of the former. On the latter point, however, evidence has accumulated to show that galactose-1-phosphate itself may be injurious to various tissues including brain, liver, lens, and kidney.[16] More recently galactose-1-phosphate has been shown to inhibit in vitro several enzyme systems concerned with glucose metabolism.[17] Such interference may constitute a specific mechanism accounting for tissue injury. Such postnatal effects of galactose-1-phosphate arouse speculation that tissues, such as the brain, might be damaged during intrauterine life. Maternal utilization of galactose is adequate under normal conditions, but it may be insufficient during pregnancy to protect the homozygous galactosemic fetus. Swarz and co-workers[18] found that galactose-1-phosphate in the cord blood of 2 newborn infants with galactosemia was several times as concentrated as in normal controls. This suggests that galactose-1-phosphate accumulates in the galactosemic fetus, at least near term. It is not known at present how other conditions

Table I. Tabulated data for the 16 living children with galactosemia including age, sex, and dietary management

Case no.	*Initials*	*Sex*	*Age*		*Race*	*Diet*	*I.Q.*
			At diagnosis	*Present*			
1	T. A.	M	14 months	11 years	White	Nutramigen	94
2	B. P.	F	5 months	10 years	White	Nutramigen	69
3	L. N.	F	5 months	10 years	Negro	Nutramigen	64
4	C. D.	M	2½ months	9 years	White	Nutramigen	94
5	R. D.	F	Newborn	7 years	White	Nutramigen	108
6	S. F.	M	3 months	9 years	White	Nutramigen	82
7	D. C.	M	6 weeks	9 years	Negro	Nutramigen	85
8	A. U.	F	15 months	6 years	White	Nutramigen	25
9	D. K.	F	Newborn	3½ years	White	Soya bean	82
10	M. B.	M	4 months	4 years	White	Nutramigen	104
11	K. M.	M	2½ months	3 years	White	Soya bean	89*
12	J. B.	F	2½ weeks	3 years	White	Nutramigen	83*
13	J. F.	F	3 months	2 years	White	Nutramigen	107*
14	R. O.†	M	2 months	2 years	White	Soya bean	70*
15	M. D.†	M	6 weeks	9 months	White	Nutramigen	93*
16	S. B.†‡	M	11 years	12 years	White	Cow's milk	11

*Developmental quotient values instead of I.Q.

†All cases except those marked by asterisks have been reported previously.

‡Reported through courtesy of Dixon State Hospital, Illinois.

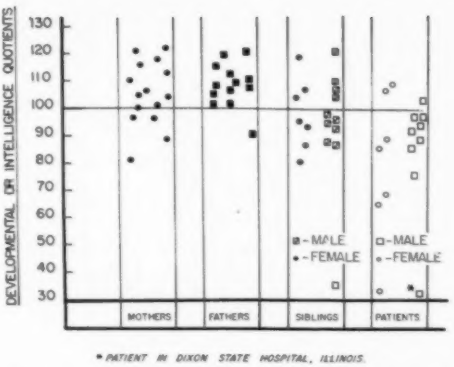


Fig. 4. Comparison of intelligence quotients of mothers, fathers, and children in 16 galactosemic families. One mother and 3 fathers were unavailable for testing.

might be modified by excluding galactose from the maternal diet. The circumstances in earlier periods of pregnancy are now under study. Data regarding fetal wastage in galactosemic carriers would be pertinent. The possible desirability should be considered of excluding galactose from the maternal diet throughout pregnancy for known heterozygous mothers.

Every child born to parents known to carry the galactosemic trait should be considered at birth as a potentially galactosemic child. Dietary restriction of galactose should be prescribed immediately and continued until the child's status as homozygote, heterozygote, or normal is determined by measurement of the galactose-1-phosphate-uridyl transferase in the erythrocytes, or by other safe means. Postnatal dietary restriction prevents physical damage and may improve the chance for satisfactory mental development. A clear indication of the adverse influence of galactose on intellectual development is given by plotting mental age against the time at which treatment was begun (Fig. 5). The children first treated at an earlier age have more favorable I.Q.'s. These results agree with isolated case reports describing severe mental malfunction in untreated galactosemic children. It is of considerable interest, however, that 2 patients of Durand[19] and the one of Ritter[20] were considered normal despite the fact that the diagnosis was not established until the ages of 14, 8, and 5 years, respectively.

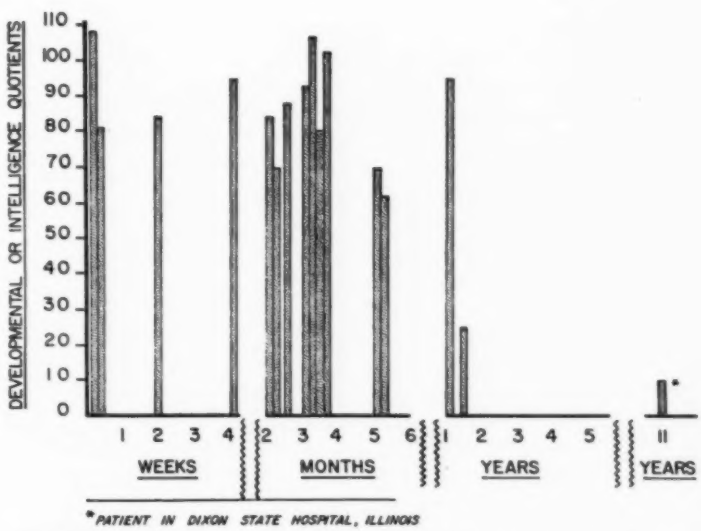


Fig. 5. Relationship between age of diagnosis and the most recent estimate of mental development.

It is evident from Fig. 4 that only 3 of the galactosemic children attained an intelligence quotient exceeding 100. Further, comparison with the intelligence quotients of parents and siblings disclosed that those of the affected children generally tended to be lower. If this is significant, the most important contributing factor might be the duration of exposure to exogenous galactose. Other possible considerations include prenatal exposure to galactose, incidental minor dietary violations, which invariably occur as children grow up, and the neonatal hyperbilirubinemia seen in some. The concentration of bilirubin in the blood is usually not markedly elevated, however, and seems unlikely as a cause of cerebral damage unless galactose-1-phosphate enhances the deleterious effect of bilirubin.

Dietary restriction of galactose may protect the brain initially, but the ultimate development of this organ may be affected adversely by rigorous and prolonged dietary restriction of galactose. Galactose is essential in the synthesis of galactolipids, the cerebrosides needed in the rapid myelination occurring in infancy and an important constituent of brain tissue throughout life. In theory, therefore, exclusion of galactose from the diet may have a deleterious effect. In practice, however, the galactose required for the synthesis of cerebrosides should be provided adequately from endogenous sources. Several enzymatic reactions have been shown to be important in the metabolism of galactose[5]:

The reaction (Reaction 3) responsible for the conversion of UDPGal to UDPGlu in the presence of a specific epimerase is reversible. In the galactosemic infant this reaction is intact and may provide an endogenous source of galactose for the synthesis of cerebrosides and other essential galactose-containing compounds. Some have advocated a more liberal diet because of the possibility of insufficient galactose from this source. The demonstration of such alternate pathways of galactose metabolism and the suggestion by some workers that galactosemic individuals develop increased tolerance to galactose with increasing age suggest the feasibility of less rigid regulation of dietary galactose. However, no such increase in tolerance could be demonstrated in galactose-loading tests of several patients in this study over a period of 5 to 10 years. Such findings do not exclude the possibility that patients may be able to metabolize small and increasing amounts of galactose, but they do indicate severe and persistent inability to cope with large loads of this sugar.

Less rigid dietary restriction of galactose would offer great psychological advantages. As galactosemic children grow older, they become more aware of their dietary restrictions. Minor personality disorders have occurred because of the need for constant attention to diet, frequent medical evaluation, and the feeling of being different from contemporaries.

Holzel[10] has cautioned against the use of soya products because they contain a

$$1)\ \text{Galactose} + \text{ATP}^{*} \xrightarrow{\text{Galactokinase}} \text{Gal-1-P} + \text{ADP}$$

$$2)\ \text{Gal-1-P} + \text{UDPGlu} \underset{}{\overset{\text{Gal-1-P uridyl transferase}}{\rightleftharpoons}} \text{Glu-1-P} + \text{UPDGal}$$

$$3)\ \text{UDPGal} \underset{}{\overset{\text{UDPGal-4-epimerase}}{\rightleftharpoons}} \text{UDPGlu}$$

*ATP = Adenosine triphosphate
Gal-1-P = Galactose-1-phosphate
ADP = Adenosine diphosphate
UDPGlu = Uridine diphosphoglucose
Glu-1-P = Glucose-1-phosphate
UDPGal = Uridine diphosphogalactose

tetrasaccharide, stachyose, which yields two molecules of galactose when hydrolyzed. There is no unanimity of opinion regarding the use of soya preparation as a milk substitute in galactosemia, primarily because it is not known whether stachyose is hydrolyzed in vivo.[21] Payne[21] feels satisfactory progress occurs in galactosemic children fed soya products. On the other hand, Schwarz[22] reports contradictory experience. Owing to the controversy regarding use of this foodstuff in galactosemia, a more detailed description of the 3 children partially reared on a soya bean formula follows.

Case 9 was given Nutramigen from birth. Her developmental quotient at 6 months of age was 96, at which time her diet was changed to a soya bean formula because of loose stools. Her developmental quotient at age 18 months was 87, and at 30 months, 82. She had been gaining weight poorly and, accordingly, Nutramigen was again prescribed. Her mother noticed an almost immediate change in her personality, and she gained 5 pounds in the next 2 months. Her D.Q. rose to 98 in a period of 6 months.

Case 11 was given Nutramigen from the age of 3 months and made rapid progress. At age 7 months his developmental quotient was 74, and at 13 months it was 96. The diet then was changed to a soya formula because he refused Nutramigen. His progress appeared satisfactory and at 30 months of age his developmental quotient was 89. At this point the soya preparation was discontinued and Nutramigen again prescribed. It is still too early to evaluate results of the dietary change.

In Case 14 the diagnosis was made at the age of 2 months and a soya formula was prescribed by the pediatrician. At 6 months of age and again at 10 months the patient's developmental quotient was 60. At this time Nutramigen was substituted for the soya preparation. When seen next at 22 months, the developmental quotient was 75. The general impression was one of greatly improved alertness and responsiveness.

Clearly, these cases permit no conclusions concerning the effects of dietary soya preparations on galactosemic children. We have the clinical impression that development is delayed by the feeding of soya preparations and, until it is proved otherwise, we do not consider soya formulas to be satisfactory as milk substitutes for the galactosemic child. Continuing studies of the accumulation of galactose-1-phosphate in erythrocytes[16] should provide a firmer basis for conclusions.

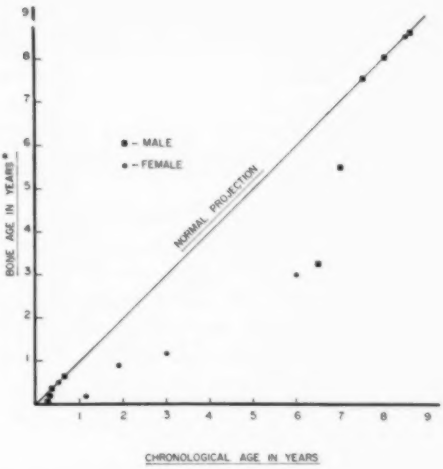


Fig. 6. Chronologic and skeletal age relationship in 15 galactosemic children.
*Greulich and Pyle standards.

As children with galactosemia have grown older, minor violations of diet have occurred, usually consisting of the ingestion of small amounts of butter, ice cream, or certain foods containing milk solids, such as bread, cookies, and chocolate candy. In only one case (No. 8), however, did major difficulties arise because of poor parental cooperation. In such instances the value and importance of monitoring the diet by periodic determination of galactose-1-phosphate in erythrocytes is obvious.

SUMMARY

Sixteen families with 15 living galactosemic children were studied. The physical growth patterns of all but 3 of the children are within normal limits. The intellectual abilities of the parents were normal. All but one of the siblings were also normal. By contrast, 4 of

the galactosemic children are mentally defective and one of them is in a state hospital for retarded children. Six others have borderline intelligence and 6 are in the low normal to normal range. Only 3 of the galactosemic children had an intelligence quotient of over 100.

Late inauguration of dietary management was associated with a greater incidence and severity of mental handicaps. Adherence to a strict galactose-free diet is suggested. It is also recommended that soya products be avoided until additional knowledge is available.

REFERENCES

1. Kalckar, H. M., Graganca, B., and Munch-Petersen, H. M.: Uridyl Transferase and the Formation of Uridine Diphosphogalactose, Nature **172:** 1038, 1953.
2. Kalckar, H. M., Anderson, E. P., and Isselbacher, K. J.: Galactosemia, a Congenital Defect in a Nucleotide Transferase. A Preliminary Report, Proc. Nat. Acad. Sc. **42:** 49, 1956.
3. Kalckar, H. M., Anderson, E. P., and Isselbacher, K. J.: Galactosemia, a Congenital Defect in a Nucleotide Transferase, Biochem. et biophys. acta **20:** 262, 1956.
4. Isselbacher, K. J., Anderson, E. P., Kurahashi, K., and Kalckar, H. M.: Congenital Galactosemia, a Single Enzymatic Block in Galactose Metabolism, Science **123:** 635, 1956.
5. Isselbacher, K. J.: Galactose Metabolism and Galactosemia, Am. J. Med. **26:** 715, 1959.
6. Anderson, E. P., Kalckar, H. M., Kurahashi, K., and Isselbacher, K. J.: A Specific Enzymatic Assay for the Diagnosis of Congenital Galactosemia, J. Lab. & Clin. Med. **50:** 469, 1957.
7. Donnell, G. N., Bergren, W. R., Bretthauer, R. K., and Hansen, R. G.: The Enzymatic Expression of Heterozygosity in Families of Galactosemics, Pediatrics **25:** 572, 1960.
8. Kirkman, H. N., and Bynum, E.: Enzymatic Evidence of a Galactosemic Trait in Parents of Galactosemic Children, Ann. Human Genet. **23:** 117, 1959.
9. Townsend, E. H., Mason, H. E., and Strong, P. S.: Galactosemia and Its Relation to Laennec's Cirrhosis, Pediatrics **7:** 760, 1951.
10. Holzel, A.: Some Aspects of Galactosemia, Mod. Probl. Pediat. **4:** 388, 1959.
11. Bernheim, M., François, R., and Mme. Ruitton-Ugliengo: Les méliturie non diabétiques chez l'enfant, Rapport au XV Congrès des Pediatres de Langue Française, Marseille, 1955.
12. Bretthauer, R. K., Hansen, R. G., Donnell, G. N., and Bergren, W. R.: A Procedure for Detecting Carriers of Galactosemia, Proc. Natl. Acad. Sc. **45:** 328, 1959.
13. Wilson, W. A., and Donnell, G. N.: Cataracts in Galactosemia, A. M. A. Arch. Opth. **60:** 216, 1958.
14. Jones, N. L., and Leak, D.: The Treatment of Congenital Galactosemia, Arch. Dis. Childhood **34:** 307, 1959.
15. Ballabriga, A., Samso, J. M., and Claret, I.: EEG et galactosémie experimentale, Mod. Probl. Pediat. **4:** 434, 1959.
16. Schwarz, V.: Metabolic Disturbances in Galactosemia, Mod. Probl. Pediat. **4:** 402, 1959.
17. Siburg, J. B., Jr.: The Enzymatic Lesions in Galactosemia, J. Clin. Invest. **36:** 929, 1957.
18. Schwarz, V., Holzel, A., and Komrower, G. M.: Laboratory Diagnosis of Congenital Galactosemia at Birth, Lancet **1:** 24, 1958.
19. Durand, P., and Semach, F.: Formes tardives, attenuées de galactosémie chez deux frères, Arch. franç. pediat. **12:** 958, 1955.
20. Ritter, J. A., and Cannon, E. J.: Galactosemia With Cataracts: Report of a Case With Notes on Physiopathology, New England J. Med. **252:** 747, 1955.
21. Payne, W. W., Prankerd, T. A. J., Wokes, E.: Treatment of Galactosemia, Lancet **1:** 336, 1960.
22. Schwarz, V., Holzel, A., Stapleton, T., and Goodell, R. A.: Treatment of Galactosemia, Lancet **2:** 1146, 1959.

Pyridium-induced methemoglobinemia

Report of a case

Richard E. Sand, M.D.,* and Chester M. Edelmann, Jr., M.D.

PORTSMOUTH, VA.

THE causes of methemoglobinemia in infancy are numerous, but can be separated readily into two groups, congenital and acquired. Congenital methemoglobinemia is a rare metabolic disorder, usually familial, of which approximately 100 cases have been reported.[1-5] Recently, several families have also been found with a rare form known as methemoglobin M disease. In contradistinction to the common form of congenital methemoglobinemia, this disease is characterized by specific abnormal hemoglobins and corresponding methemoglobin moieties with no recognized enzymatic defect in the nonhemoglobin portion of the red cell.[6, 7] Acquired methemoglobinemia is much more common than the congenital variety; hundreds of cases have been described and have been attributed to a variety of etiological agents. The purpose of this study is to alert the physician to this often-deceptive condition and to add the second instance of Pyridium-induced methemoglobinemia.

From the Pediatric Service, United States Naval Hospital, Portsmouth, Va.

The opinions expressed in this article are the private ones of the authors and not to be construed as official or reflecting the views of the Navy Department.

**Address, United States Naval Hospital, Portsmouth, Va.*

Aniline dyes from absorption of marking ink used on diapers and aniline dye derivatives, such as those used in wax crayons, dermatologic preparations, shoe polish, and various drugs, have been implicated repeatedly in the production of methemoglobinemia.[8-13] Ingestion of nitrate-contaminated well water has been noted frequently to induce methemoglobinemia in infants, in whom the decreased acidity of gastric juices permits nitrate-reducing (nitrite-producing) organisms to grow in the upper gastrointestinal tract.[14-20]

Among the more uncommon causes found in the literature are ingestion of meats with a high nitrite content,[21] accidental contamination of maple syrup with corning extract (12 per cent nitrites),[22] absorption of nitrite from a Zephiran-soaked dressing (nitrite added to retard rusting of instruments),[23] and bismuth subnitrate used in the treatment of infantile diarrhea.[24]

Dermatologic preparations such as resorcinol,[25] Benzocaine,[26-28] and synthetic bitter almond oil,[29] and systemic drugs such as sulfonamides,[30] primaquine,[31] nitrobenzene and aromatic nitro-amino compounds,[30, 32] phenytoin,[33] para-aminosalicylic acid,[34] and Lidocaine[35] have been implicated as etiological agents.

The first case of methemoglobinemia asso-

ciated with Pyridium* ingestion was disclosed in 1951 by Crawford.[36] A 3-year-old boy with exstrophy of the bladder was given Pyridium to color the urine in order to facilitate endoscopic visualization of the ureteral ostia. After 10 days of administration of Pyridium, he developed methemoglobinemia. The diagnosis was confirmed by spectrophotometric studies; he was treated with methylene blue with prompt response. Confirmation of the etiological role of Pyridium was based on the return of cyanosis and elevation of the blood methemoglobin level following a subsequent administration of the drug.

The following case is believed to be the second reported instance of Pyridium-induced methemoglobinemia, the first to follow accidental ingestion of this drug.

CASE REPORT

Present illness. This 3-year-old white female was apparently well until the day of admission when she awoke complaining of abdominal pain. Her mother noticed a blue color of her lips and hands. The patient became drowsy, slept at intervals, and continued to be lethargic the remainder of the morning. She remained essentially in the same condition until admission to the hospital, having had no respiratory distress, nausea, vomiting, diarrhea, or convulsions.

Physical examination. The temperature was 37.6° C. (rectal), pulse 140, respirations 28, and blood pressure 98/60. The patient was a well-developed, well-nourished, markedly lethargic, white female in no acute distress. Except for a peculiar slate-blue appearance, most noticeable over the face and hands, there were no other positive physical findings.

Laboratory data. Routine studies were within normal limits. The patient's venous blood was noted to have a chocolate color on withdrawal. When centrifuged, the plasma was completely clear while the red blood cell sediment retained the chocolate-brown color.

*Phenylazodiaminopyridine hydrochloride.

Therapy and course. On admission, the patient was given oxygen, but the cyanosis persisted. Therefore, methemoglobinemia was suspected. Further questioning of the mother revealed that she had found an empty medicine bottle beside the child's rocking chair. The contents subsequently were identified as Pyridium.

The patient was given methylene blue, 2 mg. per kilogram, intravenously in a 0.1 per cent solution. Within 30 minutes she was observed to be more active and within one hour was beginning to demonstrate a normal pink color. The patient showed no evidence of toxicity on the second day of hospitalization, and she was discharged with no further medication. There was no recurrence of cyanosis. She remained asymptomatic and at follow-up examinations was found to be entirely well.

DISCUSSION

Pathogenesis. Methemoglobin is a true oxide of hemoglobin, containing tri-valent iron (ferric) instead of bi-valent iron (ferrous). The oxidation of hemoglobin to methemoglobin at a slow rate can be demonstrated in normal subjects. Experimental evidence indicates that this reaction is counterbalanced by a reduction system, possibly utilizing coenzyme I and diaphorase I, which are present within red blood cells.[37] Thus, the concentration of methemoglobin in normal subjects is small, although it may vary normally from 0 to 5 per cent (0.00 to 1.9 per cent in adults, 0.00 to 2.4 per cent in infants and children, 0.00 to 2.8 per cent in full-term newborn infants, and 0.02 to 4.7 per cent in prematurely born infants.)[38]

Methemoglobinemia is a disorder in which the proportion of the hemoglobin iron in the ferric state is abnormally high, thus limiting adequate transfer of oxygen. Unlike the oxygen bound by hemoglobin, that carried by methemoglobin is so firmly bound that it is not available to the tissues.[14, 30] An absolute methemoglobin concentration of 1.5 Gm. per cent is sufficient to give the typical slate-blue or lavender cyanosis; while a level above 20 per cent of the total hemo-

globin concentration causes, in addition, the clinical symptoms of polycythemia, exertional dyspnea, and lethargy.

There is no general agreement as to the pathogenesis of methemoglobinemia. Most observations have been conducted in patients with the congenital type and indicate that the biochemical defect is in the red blood cell, consisting of an absence, deficiency, or inefficient function of the enzyme system controlling the conversion of methemoglobin to hemoglobin.[39] A deficiency of coenzyme I has been postulated to be the basic defect, although some investigators doubt that coenzyme I enters into the reaction in normal cells.[37, 40]

In contrast to the congenital defect, in the acquired variety there appears to be a normal reduction system. However, this system either is unable to compensate for a markedly increased rate of production of oxidized hemoglobin, resulting from oxidizing substances, such as nitrites; or is interfered with by toxic substances, such as aniline, and therefore is unable to continue its usual rate of hemoglobin reduction. The mode of action of Pyridium in the production of methemoglobinemia is not known.

Clinical picture and diagnosis. The signs and symptoms of methemoglobinemia vary with the level of methemoglobin, dyspnea, and cyanosis usually appearing when the concentration reaches 15 to 20 per cent. The insidious, yet fairly sudden, onset of a peculiar slate-blue cyanosis, together with a negative history of cardiac disorder in an afebrile child with no other positive physical findings except possibly minimal respiratory distress, should suggest the diagnosis of methemoglobinemia. The chocolate-brown color of venous blood (demonstrated after centrifugation to be confined to the red blood cells), the lack of response to therapeutically administered oxygen, and the dramatic response to methylene blue are confirmatory features. Absolute confirmation of the diagnosis rests on spectrophotometric identification of the pigment and quantitative determination of it, but this is rarely necessary for clinical purposes. The dark band of methemoglobin is seen at 630 to 635 mμ and disappears with the addition of 2 to 3 drops of 5 per cent potassium cyanide solution; by contrast, the sulfhemoglobin band is at 618 mμ and remains fixed after the addition of potassium cyanide.

Treatment. Methylene blue, given either intravenously or orally, is the drug of choice. Two milligrams per kilogram of body weight is given as a 0.1 per cent solution intravenously and is repeated in 2 hours if necessary. Subsequent doses are based on the clinical response and/or on blood methemoglobin levels. Although cyanosis usually clears within 1 to 2 hours following the intravenous administration, it may persist up to 24 hours with oral therapy. The mode of action of methylene blue is not certain. Available evidence suggests that the presence of methylene blue may permit the operation of an accessory reduction system incorporating the coenzyme diaphorase II.[41] Ascorbic acid may be used as an alternative or adjunctive therapeutic agent in doses of 100 to 500 mg. daily. This agent is thought to act directly on hemoglobin as a reducing agent.

SUMMARY

The second instance of Pyridium-induced methemoglobinemia, the first following accidental ingestion of this drug, is reported in a 3-year-old child. A brief review is presented of the literature of the past decade concerning the etiology, biochemistry, diagnosis, and treatment of methemoglobinemia.

REFERENCES

1. Gibson, Q. H.: Methemoglobinemia and Sulfhemoglobinemia, Biochem. Soc. Symposia **12:** 55, 1954.
2. Scott, E. M., and Hoskins, D. D.: Hereditary Methemoglobinemia in Alaskan Eskimos and Indians, Blood **13:** 795, 1958.
3. Armstrong, J. G., McKendry, J. B., and Slemon, K. W.: Methaemoglobinaemia in Infancy; Two Cases, One of Congenital and One of Acquired Variety of Methaemoglobinaemia, Canad. M. A. J. **79:** 392, 1958.
4. Newcombe, C. P.: Two Cases of Congenital Methaemoglobinaemia, Brit. M. J. **1:** 1396, 1958.
5. Lee, M. H.: Severe Congenital Methaemo-

globinaemia in an Infant, Lancet **273:** 1147, 1957.
6. Gerald, P. S., Cook, Charles D., and Diamond, Louis K.: Hemoglobin M, Science **126:** 300, 1957.
7. Pisciotta, A. V., Ebbe, S. N., and Hinz, J. E.: Clinical and Laboratory Features of Two Variants of Methemoglobin M Disease, J. Lab. & Clin. Med. **54:** 73, 1959.
8. MacMath, I. F., and Apley, J.: Cyanosis. From Absorption of Marking-Ink in Newborn Babies, Lancet **2:** 895, 1954.
9. Pickup, J. D., and Eeles, J.: Cyanosis in Newborn Babies Caused by Aniline-Dye Poisoning, Lancet **2:** 118, 1953.
10. Howarth, B. E.: Epidemic of Aniline Methaemoglobinaemia in Newborn Babies, Lancet **1:** 934, 1951.
11. Etteldorf, J. N.: Methylene Blue in Treatment of Methemoglobinemia in Premature Infants Caused by Marking Ink; 8 Cases Reported, J. Pediat. **38:** 24, 1951.
12. Stening, S. E. L.: Methaemoglobinaemia Due to Aniline, M. J. Australia **1:** 578, 1951.
13. Rieders, F., and Brieger, H.: Mechanism of Poisoning From Wax Crayons, J. A. M. A. **151:** 1490, 1953.
14. Walton, G.: Survey of Literature Relating to Infant Methemoglobinemia Due to Nitrate-Contaminated Water, Am. J. Pub. Health **41:** 986, 1951.
15. Ewing, M. C., and Mayon-White, R. M.: Cyanosis in Infancy From Nitrates in Drinking Water, Lancet **1:** 931, 1951.
16. Lecks, H. I.: Methemoglobinemia in Infancy, Am. J. Dis. Child. **79:** 117, 1950.
17. Eveloff, A. R.: Methemoglobinemia in Infants, Illinois M. J. **98:** 294, 1950.
18. Rosenfield, A. B., and Huston, R.: Infant Methemoglobinemia in Minnesota Due to Nitrates in Well Water, Minnesota Med. **33:** 787, 1950.
19. Nelson, H. G., and Sanders, H. R.: Methemoglobinemia in Infants Due to Ingestion of Nitrates in Well Water, J. Oklahoma M. A. **44:** 232, 1951.
20. Fawns, H. T., and Aldridge, A. G. V.: Methaemoglobinaemia Due to Nitrates and Nitrites in Drinking Water, Brit. M. J. **2:** 575, 1954.
21. Orgeron, J. D., Martin, J. D., Caraway, C. T., Martine, R. M., and Hauser, G. H.: Methemoglobinemia From Eating Meat With High Nitrite Content, Pub. Health Rep. **72:** 189, 1957.
22. Tepperman, J., Marquardt, R., Reifenstein, G. H., and Lozner, E. L.: Methemoglobinemic Cyanosis; Report of an Epidemic Due to Corning Extract Substituted for Maple Syrup, J. A. M. A. **146:** 923, 1951.
23. Rozenfeld, I. H.: Methemoglobinemia Resulting From Absorption of Sodium Nitrite; Report of a Case, J. A. M. A. **152:** 706, 1953.
24. Marcus, H., and Joffe, J. R.: Nitrate Methemoglobinemia, New England J. Med. **240:** 599, 1949.
25. Gasser, C.: Perakute hämolytische Innenkorperanämie mit Methamoglobinämie nach Behandlung eines Säuglingsekzems mit Resorcin, Helvet. paediat. acta **9:** 285, 1954.
26. Goluboff, N., and MacFadyen, D. J.: Methemoglobinemia in Infant, Associated With Application of Tar-Benzocaine Ointment, J. Pediat. **47:** 222, 1955.
27. Wolff, J. A.: Methemoglobinemia Due to Benzocaine, Pediatrics **20:** 915, 1957.
28. Goluboff, N.: Methemoglobinemia Due to Benzocaine, Pediatrics **21:** 340, 1958.
29. Zeitoun, M. M.: Nitrobenzene Poisoning in Infants Due to Inunction With False Bitter Almond Oil, J. Trop. Pediat. **5:** 73, 1959.
30. Bodansky, O.: Methemoglobinemia and Methemoglobin Producing Compounds, Pharmacol. Rev. **3:** 144, 1951.
31. Hansen, J. E., Cleve, E. A., and Pruitt, F. W.: Relapse of Vivax Malaria Treated With Primaquine and Report of One Case of Cyanosis Methemoglobinemia Due to Primaquine, Am. J. M. Sc. **227:** 9, 1954.
32. Mangelsdorff, A. F.: Treatment of Methemoglobinemia, A. M. A. Arch. Indust. Health **14:** 148, 1956.
33. Finch, E., and Lorber, J.: Methaemoglobinaemia in Newborn Probably Due to Phenytoin Excreted in Human Milk. J. Obst. & Gynaec. Brit. Emp. **61:** 833, 1954.
34. Claps, F. X.: Two Cases of Methemoglobinemia and Acute Hemolytic Anemia With Death Following the Ingestion of a Solution of Para-Aminosalicylic Acid, Am. Rev. Tuberc. **76:** 862, 1957.
35. Deas, T. C.: Severe Methemoglobinemia Following Dental Extractions Under Lidocaine Anesthesia, Anesthesiology **17:** 204, 1956.
36. Crawford, S. E., Moon, A. E., Jr., Panos, T. C., and Hooks, C. A.: Methemoglobinemia Associated With Pyridium Administration; Report of a Case, J. A. M. A. **146:** 24, 1951.
37. Breakey, V. K. St. G., Gibson, Q. H., and Harrison, D. C.: Familial Idiopathic Methaemoglobinaemia, Lancet **1:** 935, 1951.
38. Kravitz, H., Elegant, L. D., Kaiser, E., and Kagan, B. M.: Methemoglobin Values in Premature and Mature Infants and Children, A. M. A. Am. J. Dis. Child. **91:** 1, 1956.
39. Waisman, H. A., Bain, J. A., Richmond, J. B., and Munsey, F. A.: Laboratory and Clinical Studies in Congenital Methemoglobinemia, Pediatrics **10:** 293, 1952.
40. Waisman, H. A., Richmond, J. B., and Bain, J. A.: Enzyme Studies and Clinical Observations in Congenital Methemoglobinemia, A. M. A. J. Dis. Child. **84:** 772, 1952.
41. Kay, W. W., and MacMahon, J. F.: Idiopathic Familial Methaemoglobinaemia, Proc. Roy. Soc. Med. **46:** 717, 1953.

Spontaneous rupture of the stomach

David H. James, Jr., M.D.*

WEST MEMPHIS, ARK.

RUPTURE of the stomach in the pediatric age group is an unusual occurrence. McCormick,[1] in 1959, was able to find only 74 previously reported cases in the English literature. The vast majority of these occurred during the neonatal period. Most of them were thought to be due to one of the following causes: (1) peptic ulceration, (2) congenital deficiency of the gastric musculature, (3) injuries secondary to gavage, or (4) congestion due to septicemia or asphyxia. In a few instances, birth trauma or injudicious oxygen therapy was thought to play a role but this was difficult to evaluate.

Rarely there have appeared reports of cases of spontaneous rupture of the stomach which were ascribed to acute distention from overeating or drinking to excess.[2-5] Most of these have been in adults, but a few have occurred in children. The following case appears to fit into this category.

CASE REPORT

J. W. was a 22-month-old male infant who was entirely well, except for a slight cold, until the morning of Nov. 19, 1960. About 8:00 A.M. on this day, he was given breakfast, which consisted only of a large bowl of partially cooked rice. This rice was prepared by adding 2½ cups of water, ½ teaspoonful of salt, and ½ stick of butter to 2 cups of dry rice. This mixture was heated until all the water had evaporated (about 10 minutes). The child ate all of this and then drank at least 2 full glasses of water.

Following breakfast, he played outside for about 3 hours and then was brought in for a nap shortly before noon. At this time, nothing abnormal was noted by his parent.

Upon waking from his nap about 1:00 P.M., he was breathing quite rapidly and appeared acutely ill. He was observed at home in this condition for about 2 hours. Then he was taken to a private physician who found him to be in acute distress and referred him to Crittenden Hospital for treatment.

He was admitted to the emergency room of Crittenden Hospital shortly after 4:00 P.M. where he was found to be critically ill. He was breathing quite rapidly, almost in a gasping fashion. No peripheral pulses could be felt. The abdomen was markedly distended and tympanitic except in each flank where dullness was elicited. A fluid wave was noted.

Because of the signs of acute circulatory collapse plus some type of abdominal catastrophe, a cut-down was done and parenteral fluid and plasma were started until whole blood could be obtained. However, after

From the Division of Pediatrics, College of Medicine, University of Tennessee, and the Crittenden Memorial Hospital, West Memphis, Ark.

**Address, Crittenden Memorial Hospital, West Memphis, Ark.*

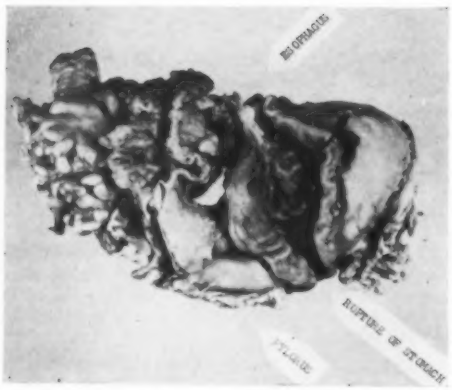


Fig. 1. Gross pathologic specimen demonstrating the tear across the anterior wall of the stomach.

about 200 c.c. of plasma had been given, the patient died.

Postmortem examination was performed about 2 hours following death. External examination revealed no evidence of trauma of any type. The significant findings were limited to the abdomen.

The peritoneal cavity contained approximately 500 c.c. of cloudy fluid and about 1½ pints of rice. Upon close inspection, it did not appear as if the rice had been cooked. However, since it had been subjected to the body fluids, it was difficult to tell about this with any certainty.

The peritoneal lining was gray with red mottling. There was some fibrin on the surface. Microscopic sections of the parietal as well as the visceral peritoneum showed the surface to be covered with fibrin in which there were many segmented neutrophils.

The stomach was found to be empty. On the lesser curvature (Fig. 1) and starting at the cardiac sphincter was a complete tear about 10 cm. in length. This extended down the lesser curvature and across the anterior wall. The edges of the tear were ragged and hemorrhagic and surrounding the tear were several particles of rice.

Microscopic sections of the stomach in the area of the tear (Fig. 2) revealed the mucosa, submucosa, and muscle coats to have ragged edges at this point. Infiltrated into the submucosa were many red blood cells as well as many pigment-filled macrophages. Also present in the submucosa were arteries which were undergoing early thrombosis. The muscle coats and serosa in the area of the tear were infiltrated by red blood cells as well as some neutrophils and the serosa contained many dilated, engorged blood

Fig. 2. Microscopic section demonstrating the congestion and infiltration of the submucosa and muscle of the stomach in the region of the tear.

vessels. There was no evidence of any ulceration, deficiency of muscle, specific infection, or malignancy.

COMMENT

It is felt that this child had a spontaneous rupture of the stomach caused by acute distention. The marked overdistention was produced by the ingestion of a large amount of partially cooked rice plus a large volume of water. It is conceivable that there may have been slight external trauma to the abdomen. History did not reveal this to be the case, however, and external examination did not disclose any sign of injury.

In most instances of spontaneous rupture, attention has been drawn to the presence of extreme gastric distention from eating or drinking to excess.[2-5] The amount ingested has usually been voluminous. In a few cases[3,4] the rupture has been precipitated by the ingestion of sodium bicarbonate following a hearty meal.

McCormick[1] reported one case of spontaneous perforation due to acute gastric dilatation in a 6-year-old boy with lipochondrodystrophy. The etiology in this case was thought to be interference with the gastric circulation.

In the majority of recorded cases[2] of spontaneous rupture, the tear has been on the lesser curvature of the stomach. One possible explanation for this is that, as the stomach becomes distended, it tends to become spherical, so that the fixed lesser curvature is called upon to withstand a relatively greater amount of stretching than the rest of the viscus.

The process of rupture begins with tearing of the mucosa. It has been suggested[2] that this may be preceded by ischemic necrosis brought about by overdistention.

SUMMARY

A case of spontaneous rupture of the stomach in a small child is reported.

The etiology of spontaneous rupture of the stomach is briefly discussed.

REFERENCES

1. McCormick, W. F.: Rupture of the Stomach in Children, A. M. A. Arch. Path. **67:** 416, 1959.
2. Millar, T. M., Bruce, J., and Patterson, J. R. Spontaneous Rupture of the Stomach, Brit. J. Surg. **44:** 513, 1957.
3. Glassman, Oscar: Subcutaneous Rupture of the Stomach; Traumatic and Spontaneous, Ann. Surg. **89:** 247, 1929.
4. Lemmon, W. T., and Paschal, G. W. Jr.: Rupture of the Stomach Following Ingestion of Sodium Bicarbonate, Ann. Surg. **114:** 997, 1941.
5. Ladkin, R. G., and Davies, J.: Rupture of the Stomach in an African Child, Brit. M. J. **1:** 644, 1948.

Dosage of chloramphenicol in premature infants

Sumner Root Ziegra, M.D.,* and Robert R. Storm, B.A.

BROOKLYN, N. Y.

PREMATURE and full-term infants treated with chloramphenicol in doses of 100 mg. per kilogram per day or higher may develop abdominal distention, loose watery stools and lethargy and may refuse feedings. In some instances the patients have developed vascular collapse and died.[1, 2, 3] We know of one infant who died in shock and in whom no cause of death was found at post mortem, who had a blood level of chloramphenicol of 195 ml. per kilogram. The symptoms usually begin on the third day after the start of therapy. The route of administration does not appear to be the determining factor since these patients received the drug intravenously, intramuscularly, or orally. It is postulated that premature infants have relatively poor liver function and are thus not able to metabolize chloramphenicol at a normal rate and consequently are particularly susceptible to intoxication from it. We have attempted to determine for premature infants the intramuscular dosage schedule which will result in blood levels generally considered effective without being excessively high.

From the Department of Pediatrics, State University of New York, Downstate Medical Center, Kings County Hospital Center, Brooklyn, N. Y.

Supported by a grant from Parke, Davis & Company.

**Present address, Department of Pediatrics, Jefferson Medical College, 1025 Walnut Street, Philadelphia, Pa.*

METHOD

Premature infants who had not previously received antibiotics were studied. The population was largely Negro and Puerto Rican. Males were studied exclusively in the first group. The remaining groups were selected at random from available premature infants with no regard to sex, color, or weight.

All blood was drawn from heel puncture. Two tenths of a milliliter of whole blood was put into 4 ml. of 0.05 per cent saponin solution to which was added 1.0 ml. of 15.6 per cent trichloracetic acid. Blood for serum was collected in sterile 3 mm. capillary tubes from the same heel puncture. The serum was separated by centrifugation and stored frozen in capillary tubes.

All chemical and microbial assays were done at the Laboratory for Clinical Investigation at Parke, Davis & Company. The chemical level of both active and inactive chloramphenicol expressed as total nitro compounds in the blood was determined by the method of Glazko and associates.[4] A microturbidimetric biologic procedure for the assay of active chloramphenicol in

serum as established by Dr. R. J. Hans and Mrs. Margaret Galbraith of that laboratory was also used.

All chloramphenicol injections were given intramuscularly in the anterior midthigh.

Dosage Group 1 consisted of 11 male infants ranging from 1 to 40 days of age with weights from 0.9 to 2.1 kilograms. They were given 25 mg. per kilogram of Chloromycetin acid succinate (a highly water-soluble sodium ester of chloramphenicol)[5] as a single dose intramuscularly. Blood was collected at 0, 3, 6, 9, 15, and 21 hours.

Table I. Dosage Group 1. Chloramphenicol blood levels (chemical assay) in premature infants following 25 mg. per kilogram Chloromycetin acid succinate given intramuscularly in a single dose

				Chloramphenicol equivalents (μg/ml.)					
Patient	*Sex*	*Age at start (days)*	*Weight at start (Kg.)*	*Preinjection control* 0 hours*	*3 hours*	*6 hours*	*9 hours*	*15 hours*	*21 hours*
Sa.	♂	1	2.1	0	27	26	21	18	17
F.	♂	4	1.8	5	22	22	19	18	11
S.	♂	4	0.9	1	26	25	21	21	18
		Mean			25	24	20	19	15
J.	♂	6	1.8	5	19	16	16	4	7
B.	♂	10	1.8	2	23	20	20	12	5
Mc.	♂	14	2.0	2	14	7	7	1	2
R. A.	♂	16	1.6	1	27	21	17	12	6
R. B.	♂	16	1.2	0	24	19	16	12	10
L.	♂	19	1.2	3	18	17	—	4	9
M.	♂	23	1.6	1	19	15	9	4	5
A.	♂	40	1.6	3	17	14	11	1	2
		Mean			20	16	14	6	6

*Nitro compounds naturally occurring in the blood.

Table II. Dosage Group 2. Chloramphenicol blood levels (chemical assay) in premature infants following 25 mg. per kilogram per day of Chloromycetin acid succinate given intramuscularly in equally divided doses every 8 hours. Blood levels drawn 4 and 8 hours after the preceding dose

				Chloramphenicol equivalents (μg/ml.)					
					First day		*Third day*		*Fifth day*
Patient	*Sex*	*Age at start (days)*	*Weight at start (Kg.)*	*Preinjection control* 0 hours*	*4 hours*	*8 hours*	*4 hours*	*8 hours*	*8 hours*
Fo.	♀	5	1.2	0	12	12	20	-	-
G.	♀	7	1.8	1	15	15	20	-	-
S.$_1$	♀	8	1.9	0	14	7	11	9	-
B. O.	♀	9	1.6	2	16	8	14	-	-
W.	♀	15	1.5	0	11	3	14	-	-
Mc.	♂	20	2.2	-	7	4	5	11	3
N.	♀	23	2.3	-	8	3	6	12	9
C.	♀	25	2.0	-	10	10	9	9	12
L.	♂	26	1.3	-	16	11	12	141†	21
S.$_2$	♂	65	2.5	-	6	10	5	8	3
Fa.	♀	66	2.0	-	6	3	5	3	8
M.	♂	72	2.9	-	6	4	5	2	1
Ba.	♂	88	3.0	-	5	5	6	4	3
		Mean			10	7	10	7	7

*Nitro compounds naturally occuring in the blood.
†Aberrant value not used in the calculations.

Table III. Dosage Group 3. Chloramphenicol blood levels (chemical and microbial assay) in premature infants following 25 mg. per kilogram Chloromycetin acid succinate and 25 mg. per kilogram Chloromycetin intramuscular given as a single dose intramuscularly in two separate sites

Patient	Sex	Age at start	Weight at start (Kg.)	*Chloramphenicol equivalents (μg/ml.)*							
				*Preinjection controls**		*24 Hrs.*		*48 Hrs.*		*72 Hrs.*	
				Chem.	*Bio.*	*Chem.*	*Bio.*	*Chem.*	*Bio.*	*Chem.*	*Bio.*
Day of birth											
J.	♀	3 hours	1.9	1	<3	33	31	24	23	10	8
W.	♀	4 hours	1.0	-	-	27	18	25	19	15	-
J.	♂	6 hours	1.9	0	<3	42	43	24	25	9	8
R. A.	♂	10 hours	1.7	0	<3	23	17	13	10	6	3
R. B.	♂	10 hours	1.6	1	<2.5	43	36	33	24	21	18
Bo.	♀	13 hours	2.0	1	-	26	21	14	10	7	4
S.	♀	14 hours	2.1	1	<3	31	29	12	9	6	3
P.	♀	16 hours	2.1	1	<1	35	23	26	18	19	10
M.	♀	17 hours	1.2	1	<3	13	9	-	-	-	-
G.	♂	18 hours	2.0	0	<1	39	35	-	-	-	-
D.	♀	18 hours	2.0	2	<3	13	7	5	2	3	<3
S.	♂	18 hours	1.2	0	-	14	12	9	5	-	-
		Mean				28	23	19	15	11	6
Second day of life											
No.	♂	32 hours	1.7	0	<3	35	39	24	20	10	8
C.	♀	33 hours	1.9	2	<3	13	12	6	6	2	<1
N.[1]	♀	35 hours	1.8	1	<3	26	25	20	27	13	9
A. A.	♀	40 hours	1.0	0	-	-	13	9	6	3	<3
A. B.	♀	40 hours	1.1	1	-	14	12	9	7	2	-
C. A.	♀	43 hours	1.9	0	<3	25	21	12	11	3	3
		Mean				23	20	13	13	6	5
H.	♀	4 days	1.8	1	3	27	16	15	7	6	2
B. A.	♀	8 days	1.8	2	1	11	8	5	6	2	3
B. B.	♀	8 days	1.8	0	1	15	13	8	6	3	3
		Mean				18	12	9	6	4	3

*Nitro compounds naturally occurring in the blood.

Dosage Group 2 consisted of 13 infants of both sexes ranging from 5 to 88 days of age and weighing from 1.2 to 3.0 kilograms. They were given Chloromycetin acid succinate, 25 mg. per kilogram per day. The drug was administered intramuscularly in divided doses every 8 hours for 5 days. Blood was collected 4 to 8 hours after the preceding dose.

Dosage Group 3 consisted of 21 infants of both sexes ranging from 3 hours to 8 days of age and weighing 1.0 to 2.1 kilograms. They were given 25 mg. per kilogram of Chloromycetin acid succinate and 25 mg. per kilogram of Chloromycetin intramuscular (an aqueous suspension of 20 micron chloramphenicol crystals)[5] in a single dose. The two medications were injected separately, one in each thigh. Blood was collected at 0, 24, 48, and 72 hours.

Dosage Group 4 consisted of 7 infants of both sexes, all less than 24 hours of age and weighing 1.6 to 2.2 kilograms. They were given 25 mg. per kilogram of Chloromycetin acid succinate and 25 mg. per kilogram of Chloromycetin intramuscular intramuscularly. Injection sites in opposite thighs were selected so that there was no mixing of the two products. The dose was repeated once in 48 hours. Blood was collected at 0, 24, 48, 72, 96, and 120 hours.

RESULTS

Dosage Group 1. Eleven infants who received 25 mg. per kilogram of Chloromycetin acid succinate intramuscularly had a mean blood level of chloramphenicol equivalents by chemical determination of 21 μg per milliliter in the first 3 hour sample with a range of from 14 to 27 μg per milliliter. Three infants 4 days old and younger maintained a mean blood level of 15 μg with a range of 11 to 17 μg per milliliter for at least 21 hours. A mean blood level of 14 μg with a range of 7 to 20 μg per milliliter was found in 8 older premature infants, 6 to 40 days of age, for at least 9 hours (Table I).

Dosage Group 2. Thirteen infants ranging in age from 5 to 88 days given 25 mg. per kilogram per day of Chloromycetin acid succinate in divided doses every 8 hours intramuscularly had a mean blood level by chemical determination of 10 μg per milliliter 4 hours after the preceding dose with a range of 5 to 16 μg per milliliter. Thirteen of 26 determinations indicated levels below 10 μg. The mean blood level on samples obtained at 8 hours after each dose was 7 μg with 19 of 28 determinations below 10 μg per milliliter (Table II).

Dosage Group 3. Twenty-one infants who received 25 mg. per kilogram of Chloromycetin acid succinate and 25 mg. per kilogram of Chloromycetin intramuscular as a single dose were divided into three subgroups on the basis of age. Twelve infants from 3 to 18 hours of age had a mean blood level by chemical determination of 28 μg with a range of 13 to 43 μg per milliliter after 24 hours and a mean of 19 μg with a range of 5 to 33 μg per milliliter after 48 hours. Six infants in the second day of life, 32 to 43 hours of age, had a mean of 23 μg with a range of 13 to 35 μg per milliliter after 24 hours and a mean of 13 μg with a range of 6 to 24 μg per milliliter after 48 hours. Three infants 4 to 8 days of age had a mean of 18 μg with a range of 11 to 27 μg per milliliter in 24 hours and a mean of 9 μg with a range of 5 to 15 μg per milliliter after 48 hours. Microbial assays performed on corresponding blood sera confirmed the above chemical findings (Table III and Fig. 1).

Dosage Group 4. Seven infants ranging in age from 3 to 21 hours were given 25 mg. per kilogram of Chloromycetin acid succinate and 25 mg. per kilogram of Chloromycetin intramuscular. This dose was repeated in 48 hours. The mean blood levels by chemical determination show a mean

Table IV. Dosage Group 4. Chloramphenicol blood levels (chemical and microbial assay) in premature infants following 25 mg. per kilogram Chloromycetin acid succinate and 25 mg. per kilogram Chloromycetin intramuscular given as a single dose intramuscularly in two separate sites repeated once only at 48 hours

Patient	Sex	Age at start (hours)	Weight at start (Kg.)	Chloramphenicol equivalents (μg/ml.)											
				Preinjection controls*		24 Hours		48 Hours		72 Hours		96 Hours		120 Hours	
				Chem.	Bio.	Chem.	Bio.	Chem.	Bio.	Chem.	Bio.	Chem.	Bio.	Chem.	Bio.
				First dose				Second dose							
S.	♂	3	1.6	1	<3	17	13	11	9	34	29	20	17	10	8
B. A.	♂	6	2.2	2	<3	16	11	9	7	30	27	15	15	6	5
B. B.	♀	6	1.6	2	<3	8	6	6	4	21	21	11	6	2	2
J. A.	♀	9	2.1	0	<3	29	34	21	29	22	24	9	8	2	3
A.	♂	14	2.2	0	<3	30	30	19	14	27	31	16	14	5	3
J.	♂	16	1.8	0	<3	24	27	20	18	32	35	14	15	2	3
M.	♀	21	1.6	0	<3	35	38	27	26	50	48	37	35	20	18
Mean						23	23	16	15	32	31	17	16	7	6

*Nitro compounds naturally occurring in the blood.

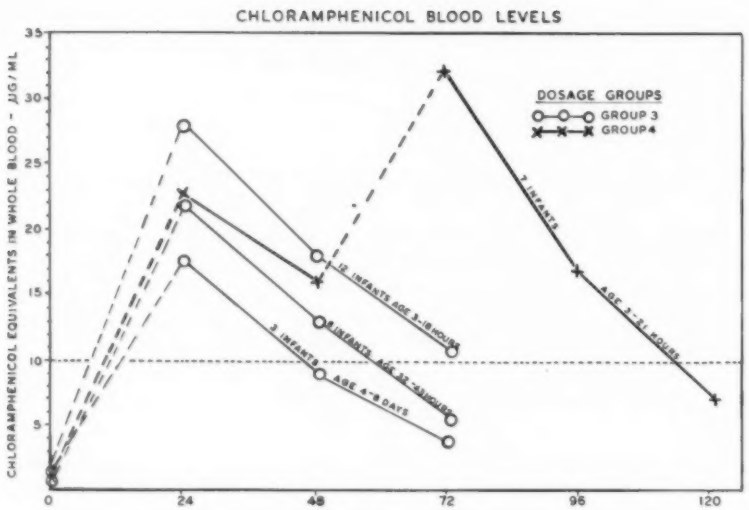


Fig. 1. Chloramphenicol equivalents in whole blood of premature infants (Dosage Group 3) following 25 mg. per kilogram Chloromycetin acid succinate and 25 mg. per kilogram Chloromycetin(R) intramuscular, both given intramuscularly in a single dose: *age 3 to 18 hours, mean of 12 infants; age 32 to 43 hours, mean of 6 infants; age 4 to 8 days, mean of 3 infants.*

In Dosage Group 4 the same two forms of chloramphenicol are used as in Group 3 except that the dose was repeated at 48 hours. *Age 3 to 21 hours, mean of 7 infants.*

of 23 µg with a range of 8 to 35 µg per milliliter after 24 hours and a mean of 16 µg with a range of 6 to 27 µg per milliliter after 48 hours. Twenty-four hours following the second dose they had a mean blood level of 32 µg with a range of 21 to 50 µg per milliliter. Forty-eight hours after the second dose their mean blood level was 17 µg with a range of 9 to 37 µg per milliliter. Microbial assays performed on corresponding blood sera confirmed the above chemical findings (Table IV and Fig. 1).

No abdominal distention, loose stools, lethargy, refusal of feeding, or circulatory collapse was seen in any of these premature infants.

DISCUSSION

Serious sequelae to the use of chloramphenicol have been reported in premature infants who have received large doses (100 mg. per kilogram per day). It has been postulated that these bad results are secondary to the high levels of circulating chloramphenicol which reflect the slower rate of metabolism of the drug (inactivation by conjugation to glucuronic acid) and to a slower rate of renal excretion. We feel that, with an adjustment in dosage, effective blood levels (10 µg per milliliter)[6, 7, 8] can be maintained and that blood levels now thought to be sufficient to cause toxic symptoms will not be reached.

It appears that older premature infants are able to excrete chloramphenicol at a more rapid rate than can the newly born, since our mean blood levels were consistently lower in the older infants (Fig. 1). When Chloromycetin acid succinate alone was administered to Dosage Group 1 infants, an effective blood level was maintianed in all infants under 4 days of age for at least 21 hours, whereas only 1 of 8 infants over 6 days of age had an effective level at

that time. Likewise, in Dosage Group 3, 8 of 10 infants 18 hours of age and younger had an effective blood level after 48 hours and only 1 of 3 infants 4 days or older maintained a blood level over 10 μg per milliliter.

In young infants of Group 1, effective blood levels were attained within 3 hours after administration of Chloromycetin acid succinate. In young infants of Groups 3 and 4, effective levels were maintained for at least 48 hours after administration of a combination of Chloromycetin acid succinate and Chloromycetin intramuscular. No signs of toxicity were encountered and blood values were not unduly high. For these reasons we recommend that newly born premature infants less than 1 day of age be given a dose of 25 mg. per kilogram of Chloromycetin acid succinate and 25 mg. per kilogram of Chloromycetin intramuscular, administered intramuscularly, to be repeated in 48 hours.

Our data do not allow us to recommend the same dosage schedule for premature infants over 4 days of age, but we believe that effective blood levels would be maintained if the dose recommended for newly born premature infants was given every 24 to 36 hours. This dose would be at the most, 50 mg. per kilogram per day and is well below the dosage where toxic symptoms have been reported in premature infants of this age.

SUMMARY

1. Chloromycetin acid succinate in a dose of 25 mg. per kilogram per day appears to be insufficient to maintain effective blood levels in premature infants if given intramuscularly in divided doses every 8 hours.

2. Chloromycetin acid succinate, 25 mg. per kilogram per day, given in a single dose intramuscularly produces effective blood levels within 3 hours which persist for at least 9 hours in premature infants, but only rarely for 21 hours in infants over 6 days of age.

3. A good method of administering chloramphenicol to newly born premature infants to maintain an effective and not unduly high blood level is with a dose of 25 mg. per kilogram Chloromycetin acid succinate and 25 mg. per kilogram of Chloromycetin intramuscular given intramuscularly in separate syringes; these administrations are repeated in 48 hours. None of the infants thus treated in the present study manifested toxic symptoms.

4. Premature infants over 4 days of age may require the same dosage every 24 to 36 hours to maintain similar levels. Further study will be necessary to confirm this assumption, however.

REFERENCES

1. Sutherland, J. M.: Fatal Cardiovascular Collapse in Infants Receiving Large Amounts of of Chloramphenicol, A. M. A. J. Dis. Child. **97:** 761, 1959.
2. Burns, L. E., Hodgeman, J. E., and Cass, A. B.: Fatal Circulatory Collapse in Premature Infants Receiving Chloramphenicol, New England J. Med. **261:** 1318, 1959.
3. Experience of the Department of Pediatrics, State University of New York, Downstate Medical Center (unpublished).
4. Glazko, A. J., Wolf, L. M., and Dill, W. A.: Biochemical Studies on Chloramphenicol (Chloromycetin). 1. Colorimetric Methods for Determination of Chloramphenicol and Related Nitro Compounds, Arch. Biochem. **23:** 411, 1949.
5. Weiss, C. F., Glazko, A. J., and Weston, J. K.: Chloramphenicol in the Newborn Infant. A Physiologic Explanation of Its Toxicity When Given in Excessive Doses, New England J. Med. **262:** 787, 1960.
6. Welch, H.: Chloramphenicol, in Principles and Practice of Antibiotic Therapy, New York, 1954, Medical Encyclopedia, Inc., chap. 9, pp. 21-24, 205-229.
7. Felix, N. S.: Chloramphenicol; Applied Pharmacology, Pediat. Clin. North America **3:** 317, 1956.
8. Florey, M. E.: Chloramphenicol, in The Clinical Application of Antibiotics, London, 1957, Oxford University Press, vol. 3, chap. 1, pp. 1-17.

TROPICAL PEDIATRICS

Acute infantile beriberi

D. H. S. Reid, M.B., Ch.B., Captain, R.A.M.C.*

FEW conditions give rise to such a varied clinical picture as infantile beriberi. The syndrome has been divided into acute, subacute, and chronic forms and into gastrointestinal, cardiorespiratory, and meningitic phases,[1, 2, 3] but the clinical features of any one case may include any combination or permutation of these types. For this reason it may be worth while to report 4 cases of the syndrome seen in Gurkha infants in Hong Kong showing a constant clinical pattern which may represent yet another complex of the kaleidoscopic picture.

CASE REPORTS

Case 1. Balbahadur L., a 6-week-old, breast-fed Gurkha boy, was admitted because he had suddenly become acutely ill 3 hours earlier. For the previous day he had been fretful and had regurgitated some of his feedings. Past history and family history were otherwise negative.

On examination, he was well nourished and not dehydrated, but was comatose, dyspneic, cyanosed, and in a state of collapse. The temperature was 97.0° F., the pulse rate was 148 per minute, and the respirations were 54 per minute. Respirations were rapid and labored, with the use of ancillary muscles of respiration, and with subcostal, supraclavicular, and intercostal indrawings. A striking feature was a curious expiratory grunt. It appeared as if breathing was momentarily held at full inspiration followed by a prolonged, difficult, grunting expiration. The chest was otherwise clear. The extremities were cold, and the peripheral pulses were poor in volume. The heart sounds were faint, but there was no significant hepatomegaly or other sign of heart failure. He was comatose, with a glazed appearance of the eyes, lying limp with flaccid limbs and diminished tendon reflexes.

Laboratory data. The hemoglobin level was 65 per cent; leukocyte count was 8,600 per cubic millimeter (lymphocytes 74 per cent). Blood films revealed no malarial parasites. The Mantoux test was negative. Stools, urine, and chest x-ray showed no abnormality. In the mother's blood, pyruvic acid, estimated by the method of Friedemann and Haugen,[4] was 1.84 mg. per 100 ml. (normal value 0.5 to 1.0 mg. per 100 ml.), and the blood thiamine level, determined by the method of Friedemann and Kmieciak,[5] was 4.1 μg per 100 ml. (average value 5.70 μg per 100 ml.).

Progress and treatment. The infant was taken off breast feeding and was treated with thiamine (100 mg. intramuscularly), oxygen, and penicillin. His condition rapidly improved, the expiratory grunt softened to a moan, and later to a faint, plaintive whine. Breathing became noiseless and effortless

From the British Military Hospital, Hong Kong.

**Present address, The Children's Hospital of Philadelphia, 1740 Bainbridge Street, Philadelphia 46, Pa.*

within 3 hours. He was subsequently removed from the oxygen tent, and after 8 hours he had completely recovered and appeared a normal, healthy, happy child. Breast feeding was resumed after adequate amounts of thiamine had been given to his mother who showed no obvious signs of beriberi.

Case 2. Satabel G., a 6-week-old, breast-fed Gurkha boy, was admitted with a history of slight vomiting and diarrhea for 2 days, and anorexia and oliguria for the previous day. The night before, he did not appear well and his eyes had a glazed appearance. He was seen by a medical officer who gave single injections of penicillin and chloramphenicol. The next morning he became acutely ill.

On examination, he was well nourished, dyspneic, comatose, and cyanosed. The temperature was 98.0° F., the pulse was 140 per minute, and the respirations were 60 per minute. Respirations were rapid with difficult, grunting expiration, and subcostal retraction. The chest was clear except for the conducted laryngeal sounds. The extremities were warm, the peripheral pulses and heart sounds were good, and there were no signs of heart failure. He lay comatose, limp, and flaccid, but, if handled, he might momentarily arch his head backwards, flex his arms, and extend his lower limbs. The tendon reflexes were brisk.

Laboratory data. The hemoglobin level was 65 per cent; leukocyte count was 8,000 per cubic millimeter (lymphocytes 74 per cent). The Mantoux test was negative. Stools, urine, and chest x-ray showed no abnormality.

Progress and treatment. The infant was taken off breast feeding. He received thiamine (100 mg. intramuscularly) and was placed in an oxygen tent. He improved visibly with this therapy, expiratory grunts faded to a faint moan and plaintive whine, and breathing became noiseless and effortless within 2 to 3 hours. At 4 to 5 hours on removal from the oxygen tent he appeared quite normal, unperturbed, and hungry. He began to nurse and passed urine for the first time that day. Large amounts of thiamine were given to the mother before breast feeding was re-established. She had been avoiding eating vegetables and had been existing largely on rice and tea since the baby's birth, but showed no overt signs of beriberi.

Case 3. Limbu M., an 8-week-old, breast-fed Gurkha girl, was admitted because she had suddenly become acutely ill 2 hours previously. There had been slight vomiting on one or two occasions during the past day but her past history and family history were otherwise negative.

On examination, she was well nourished, dyspneic, semicomatose, and cyanosed. The temperature was 98.0° F., pulse was 160 per minute, and the respirations were 50 to 60 per minute. Breathing was rapid and difficult, with prolonged, forced, grunting expirations, but the chest was otherwise clear.

The extremities were warm, peripheral pulses and heart sounds were of good quality, and no hepatomegaly or other signs of heart failure were noted. The head and eyes were turned upward and to the right, and the eyes had a glazed appearance. The coma was not complete, and she took a momentary interest in her surroundings if disturbed. The limbs were hypotonic but tendon reflexes were normal.

Laboratory data. Hemoglobin level was 94 per cent; leukocyte count was 18,000 per cubic millimeter (polymorphonuclear leukocytes 63 per cent; lymphocytes 37 per cent). The Mantoux test was negative. Stools, urine, and chest x-ray showed no abnormality. Urine tests for phenylpyruvic acid were negative.

Treatment in hospital. The infant was taken off breast feeding and was treated with thiamine (50 mg. intramuscularly), oxygen, and penicillin. Recovery was dramatic and she appeared quite undisturbed when removed from her oxygen tent 4 hours later. The mother showed no signs of beriberi, but breast feeding was not resumed until she had received adequate amounts of thiamine.

Case 4. Bhimbahadur G., a 3-month-old, breast-fed Gurkha girl, was admitted with a history of screaming episodes, slight diar-

rhea, and mild cough. She was well nourished, with mild coryza, slightly irritable, and restless but appeared well otherwise. Breast feeding was continued and no treatment was given to mother or infant. Twenty-four hours later she suddenly became acutely ill and moribund in the hospital.

On examination, she was dyspneič, cyanosed, comatose, and in a state of collapse. The temperature was 96.4° F., the pulse rate was 160 per minute, and the respirations were 60 per minute. Respirations were rapid and distressed, with use of accessory muscles of respiration and with subcostal, supraclavicular, and intercostal retractions. There were inspiratory stridor and expiratory grunts, but the chest was otherwise clear. The inspiratory stridor was of a peculiar type as if the walls of the larynx had collapsed at the end of expiration and during the first part of inspiration were being "sucked apart." The extremities were cold and clammy, the pulse was weak and thready, and heart sounds were faint. She was comatose and unresponsive; there were conjugate elevation and hippus of the eyes with ptosis of the left upper eyelid. The limbs were hypotonic.

Laboratory data. The hemoglobin level was 80 per cent; leukocyte count was 12,000 per cubic millimeter (polymorphonuclear leukocytes 62 per cent; lymphocytes 38 per cent). Blood films showed no malarial parasites. Blood sugar and electrolytes were normal. The Mantoux test was negative. Stools, urine, cerebrospinal fluid, and x-rays of larynx and chest showed no abnormality.

Progress and treatment. Breast feeding was stopped. The infant received thiamine (150 mg. intramuscularly), oxygen, penicillin, chlortetracycline, and hydrocortisone (25 mg. intramuscularly). A dramatic improvement occurred, and she appeared quite normal in less than 10 hours, apart from evidence of the previous slight cold. The history obtained from the mother later revealed that since the birth of the child she had not eaten green vegetables "for fear of giving the baby green diarrhea," but had been existing on curry and boiled white rice. No signs of beriberi were noted in the mother who, nevertheless, was given adequate amounts of thiamine before resumption of breast feeding.

DISCUSSION

Clinical features. The manifestations of infantile beriberi are so extensive and varied that the condition must be suspected in any ill infant in any part of the tropics where rice is the staple; it is beyond the scope of this paper, however, to attempt to describe the kaleidoscopic picture in detail. In brief, the acute form of the disease generally presents as sudden death or as one of three syndromes: cardiorespiratory, meningitic, or gastrointestinal.[3] The clinical picture of the 4 cases reported here contains features of all three of these syndromes, and may represent yet another manifestation in the broad spectrum of clinical patterns of the condition.

These 4 babies represent the cases of infantile beriberi seen in this hospital in the last 18 months. During this period no infant died from the disease after admission but frequently, however, similar patients died before arrival or were found dead at home. The similarity of clinical and pathologic features might suggest that these cases of sudden death were also due to beriberi.

From the descriptions given, a clear-cut clinical pattern is evident: (1) All the infants were breast fed without complementary feeding of any kind. (2) Time of onset was from 6 to 12 weeks of age. (3) The infants were well nourished in appearance. (4) Initial or premonitory symptoms were minimal: anorexia, vomiting, diarrhea, recent failure to gain weight, irritability, a glazed appearance of eyes, were inconstant findings. (5) Onset was acute with either sudden death or sudden illness in a previously apparently well child.

Description of the acute attack. The acute illness had certain characteristic, but puzzling features which might suggest to the inexperienced physician a mixed diagnosis of encephalitis, respiratory disorder, and cardiac failure. The temperature was normal or subnormal. Cyanosis was central in origin, and

was not marked, being seen more as a pale blue discoloration of lips, circumoral region, and extremities. Dyspnea of an unusual type was evident. The distinctive feature was a curious expiratory grunt. It appeared as if breathing was momentarily held at full inspiration, followed by a prolonged, difficult, grunting expiration. The expiratory interval was only relatively prolonged in proportion to inspiration and, with the degree of tachypnea, must have been extremely short. The fourth and most severely affected infant had inspiratory stridor as described. Accessory muscles of respiration might be used, and subcostal, supraclavicular, and intercostal retractions might be present. The chest was clear, except for conducted laryngeal sounds. The expiratory grunt faded to a plaintive whine and later to a faint moan, as recovery with treatment occurred.

The peripheral pulses and heart sounds were good in 2 of the infants, but collapse and peripheral circulatory failure occurred in the other 2; there were cold extremities, poor peripheral pulses, and faint heart sounds. Hepatomegaly and other signs of congestive heart failure were not conspicuous features in this series.

Coma was present in each of the 4 cases. Limbs were generally hypotonic but tendon reflexes were variable. Other features, such as conjugate deviation of the eyes, were occasionally present but were not essential for the diagnosis.

LABORATORY DATA. The infants were too ill for instigation of laboratory and other technical procedures until some improvement in their condition had taken place, and radiologic examination of the chest in particular was not performed until recovery had occurred. The Mantoux tests were negative. Examination of blood, cerebrospinal fluid, urine and stool, and x-rays of chest and larynx showed no abnormality except for a mild anemia in 2 infants. The pyruvic acid level in the mother's blood in the first infant was abnormally high, and the thiamine level was low. These biochemical estimates were not available at the time of the illness of the other infants.

Diagnosis. Diagnosis rested on the distinctive clinical picture and on the rapid and complete response to treatment within a few hours. The virtual disappearance of the disease in Gurkha infants in Hong Kong with the use of prophylactic thiamine, when formerly it had been prevalent, is added confirmation that these were cases of beriberi. The differential diagnosis included encephalitis, infectious croup, spasmodic bronchitis, pneumonia, septicemia, and other acute diseases seen in infants but did not prove difficult with the characteristic clinical picture described in this condition.

The most striking features of acute infantile beriberi are the sudden onset of the disease and the rapid recovery with treatment. Andrews,[6] Bray,[7] Fehily,[2] Sato,[8] Sharma,[9] and Trowell and Jelliffe[3] emphasize the acuteness of onset, the frequency of sudden death, and the variety of manners of presentation. Sato[8] regards sudden death as "the most typical symptom" of infantile beriberi. Although not every case of acute fulminating infantile beriberi may respond to even massive doses of thiamine,[8] the rapidity of recovery, when it does occur, is virtually diagnostic. Trowell and Jelliffe[3] state that "the only practical test for the diagnosis of infantile beriberi is the therapeutic one of giving an injection of thiamine. Improvement will be noted within a few hours and should be progressive; sometimes it is dramatic." The rapidity of recovery following the administration of thiamine to the patients described here is strongly suggestive that their condition, known as the "Gurkha syndrome" of Gurkha infants in Hong Kong, was infantile beriberi and was thus identical with "Fung Taam" of Chinese babies in Hong Kong, with "Kakke" in Japan, with "Taon" in the Philippines, and with "Tha Nge Na" in Burma.

Necropsy findings. Frequently specimens have had to be examined in imperfect condition because of the delay in transport and consequent deterioration in this warm climate. With these limitations, Noble[10] has performed many postmortem examinations of infants whose death was attributed to in-

Fig. 1. Dependent edema in a Gurkha woman who manifested other signs of cardiovascular beriberi.

fantile beriberi and of Gurkha infants of the same age group who died suddenly at home. In each group he has been impressed by the absence of any significant pathologic lesions to account for death. Other workers have reported similar autopsy observations.[2]

Treatment. The first steps in treatment were the cessation of breast feeding and the adoption of artificial feeding until the baby had recovered, and the mother's thiamine deficiency had been corrected. Thiamine was given by injection to the infant, and oxygen was needed in the acute state. Because of the possibility of lowered resistance during the acute stage to secondary bacterial invasion, an antibiotic was generally given.

During the past 12 months the disease has disappeared with the large-scale prophylactic use of thiamine among the Gurkha mothers and infants. Thiamine had not been administered in the one case which occurred during this time. Prior to this time there were more than 12 deaths per year.

Pathogenesis. The study of the pathogenesis of beriberi is the study of the interaction between man and rice.[11] The Gurkha families receive highly milled rice, and, moreover, a minority of Gurkha mothers superstitiously restrict their diet to curry and rice for some months after the birth of the infant; the second and fourth cases are such examples. The frequency of restriction of the maternal diet in the postnatal period in the countries where beriberi is seen has been observed widely.[9, 12] Furthermore, there is some evidence[12] that beriberi is becoming more frequent in rice eating countries where, with increasing prosperity, white, polished rice is increasingly consumed.

An unexpected aspect of the condition is the frequent absence of clinical beriberi in the mothers feeding babies in this age group. The reason may be as Fehily[1] states "with the advance of maternal avitaminosis milk secretion diminishes and eventually stops entirely." Latent beriberi as evidenced by a raised blood pyruvic acid level certainly existed in some nursing Gurkha mothers before they began to receive thiamine prophylactically. Frank beriberi was not uncommon in other Gurkha families before the widespread use of thiamine prophylactically; an example is illustrated in Fig. 1.

Although exceptions to this concept occur,[13] breast feeding is generally regarded as the sine qua non for the development of infantile beriberi.[14] It is believed that the condition is due not so much to a simple deficiency of thiamine in the breast milk as to an acute poisoning from the accumulation in the milk of various highly toxic intermediate products of carbohydrate metabolism, such as methylglyoxal resulting from thiamine deficiency in the mother.[1, 2, 8] Since thiamine is required for the oxidative breakdown of carbohydrate (the main source of energy in a healthy baby[15]) and the amount of vitamin needed is in proportion to the amount of carbohydrate metabolized, the "well-fed" baby, whose feedings of breast milk are deficient in thiamine, is burdened with a larger amount of carbohydrate and thus also of these toxic products and is more liable to acute attacks and sudden death. The "underfed" baby whose energy supplies are lower and met more by body fat and in whom there may be deficiency of other nutrients will be more likely to suffer from the subacute or chronic forms.[1] The age at onset of the acute form of infantile beriberi is from the first to the fourth month of life.

The infant is believed to have sufficient reserves for the first month of life.[1] After the fourth month the clinical syndrome tends to be subacute or chronic, although the acute form may occur at this time also.[14]

Infantile beriberi does not seem to mimic the adult form and the difference in the mode of presentation may give support to the hypothesis of breast milk intoxication.

SUMMARY

Four cases of acute infantile beriberi with similar clinical features are presented. The infants were breast fed, well nourished, and from 6 to 12 weeks of age.

Premonitory symptoms were inconspicuous and the acute illness occurred suddenly in a previously apparently well child. The features of the acute attack were coma, dyspnea, and cyanosis. The dyspnea was distinctive with a curious expiratory grunt. Peripheral circulatory failure occurred in 2 of the cases. The limbs were hypotonic, but reflexes were variable.

Treatment consisted of the cessation of breast feeding until thiamine had been given to the mother, and the administration of thiamine, oxygen, and an antibiotic to the infant. Recovery was dramatic, taking place within a few hours. The disappearance of this condition in Gurkha infants in Hong Kong with the use of thiamine prophylactically is mentioned.

My thanks are due to Dr. R. G. Mitchell, Royal Infirmary, Dundee, Scotland, and to Lieutenant D. T. D. Hughes, R.A.M.C., B. M. H., Hong Kong, for their valued help in the preparation of this paper; to Dr. S. C. Hu and Dr. C. C. Wong of the Department of Pediatrics and Medicine, University of Hong Kong, Dr. C. Elaine Field of the General Hospital, Singapore, and Professor D. B. Jelliffe of the Medical School, University College of East Africa, Kampala, Uganda, for their advice; and to the Director-General, Army Medical Services.

The pyruvic acid and thiamine estimations on Case 1 were performed by the Department of Chemical Pathology, University of Hong Kong.

REFERENCES

1. Fehily, L.: Infantile Beriberi in Hong Kong, J. Trop. Med. **44:** 21, 1941.
2. Fehily, L.: Human-Milk Intoxication Due to B_1 Avitaminosis, Brit. M. J. **2:** 591, 1944.
3. Trowell, H. C., and Jelliffe, D. B.: Diseases of Children in the Subtropics and Tropics, London, 1958, Edward Arnold & Co., p. 194.
4. Friedemann, T. E., and Haugen, G. E.: Pyruvic Acid. II. The Determination of Keto Acids in Blood and Urine, J. Biol. Chem. **147:** 415, 1943.
5. Friedemann, T. E., and Kmieciak, T. C.: Determination of Thiamin in Blood, J. Lab. & Clin. Med. **28:** 1262, 1943.
6. Andrews, V. L.: Infantile Beriberi, Philippine J. Sc. **7B:** 67, 1912.
7. Bray, G. W.: Vitamine B Deficiency in Infants: Its Possibility, Prevalence and Prophylaxis, Tr. Roy. Soc. Trop. Med. & Hyg. **22:** 9, 1928.
8. Sato, A.: The Most Typical Symptom of Infantile Beriberi, Preliminary Report, Tohoku J. Exper. Med. **55:** 1, 1951.
9. Sharma, C.: Mother, Child and Nutrition, J. Trop. Pediat. **1:** 47, 1955.
10. Noble, J. E.: Personal communication, 1959.
11. Follis, R. H.: Nutritional Disease, in Proc. Conference on Beriberi, Endemic Goiter and Hypovitaminosis A, Fed. Proc. **17:** Supp. 2, 1958.
12. Burgess, R. C.: Nutritional Disease, in Proc. Conference on Beriberi, Endemic Goiter and Hypovitaminosis A, Fed. Proc. **17:** Supp. 2, 1958.
13. Haridas, G.: Infantile Beriberi in Singapore During the Latter Part of the Japanese Occupation, Arch. Dis. Childhood **22:** 23, 1947.
14. Ramalingaswami, V.: Nutritional Disease, in Proc. of a Conference on Beriberi, Endemic Goiter and Hypovitaminosis A, Fed. Proc. **17:** Supp. 2, 1958.
15. Evans, P. R., and MacKeith, R.: Infant Feedings and Feeding Difficulties, ed. 2, London, 1954, J. & A. Churchill, Ltd., p. 41.

MEDICAL PROGRESS

Recognition and investigation of hypoglycemia

Alexis F. Hartmann, Sr., M.D.,* Hulda J. Wohltmann, M.D., and Jean Holowach, M.D.

ST. LOUIS, MO.

FROM our experience with children with hypoglycemia during the past 35 years, we have come to feel that the disease is often not recognized before considerable brain damage has occurred. Early positive diagnosis and understanding of the etiology of hypoglycemia demand a high index of suspicion, proper laboratory evaluation, and a methodical plan of study. Suspicion of its possibility should be aroused both by the clinical picture and by circumstances judged favorable to its development, even in the absence of clear-cut signs or symptoms. The latter is especially true of newborn or very young infants and of children who have had many episodes of hypoglycemia and who seem to have acquired some tolerance for it.

The clinical picture seems dependent on quite a number of factors, such as age, duration of the hypoglycemia, its etiology, associated brain or other organ damage, associated acute illness or other metabolic disturbances, associated anticonvulsive therapy, as well as on the actual concentration of the blood glucose. The very common hypoglycemia seen a few hours after birth in normal infants, especially, those born of mothers who had diabetes[1] (Fig. 1) is often overlooked because the only symptoms might be slight cyanosis, some degree of lethargy, and some degree of subnormal temperature, symptoms so often noted in nonhypoglycemic newborn infants. If the blood sugar reaches zero, however, and remains there for any length of time (such as an hour or more), one should expect the more serious manifestations of apnea and convulsions. In such infants, administration of glucose or such hyperglycemic agents as adrenalin or glucagon cannot always be used as a therapeutic test of the presence of hypoglycemia. In general, the symptoms of hypoglycemia of short duration respond dramatically to restoration of a normal blood sugar, but those of longer duration often respond quite slowly and unimpressively. Sometimes failure

From the Department of Pediatrics, Washington University School of Medicine and the St. Louis Children's and Maternity Hospitals.

**Address, Department of Pediatrics, Washington University School of Medicine, 500 South Kingshighway, St. Louis 10, Mo.*

of response can be attributed to concomitant brain damage other than that produced by hypoglycemia, sometimes to associated adrenal involvement. In other cases, however, just the effect of prolonged absence of glucose from the brain cells seems responsible. Geiger's[2] observations on cat brain deprived of glucose come to mind, because of their pertinence. Not infrequently a number of conditions are operating simultaneously in seriously ill young infants, any one of which could give rise to symptoms often seen in hypoglycemia: hypocalcemia, alkalosis, hypo- or hypernatremia, and cerebral edema. One of the most interesting and bizarre pictures of this kind was seen in the infant born with severe hyperthyroidism described by Koerner.[3] When one of us (A. F. H.) was consulted about this infant shortly after his birth, because of perinatal circumstances, hypoglycemia was predicted and a blood sugar of zero developed at 8 hours of age. The knowledge of an unusually high cord blood sugar at birth had frequently been a reliable prognosticator of severe hypoglycemia a few hours later,[1] and so had the knowledge of intracranial birth trauma, especially when associated with adrenal hemorrhage. Occasionally, the side effects of overdosage of phenobarbital and Dilantin have seemed to accentuate or complicate hypoglycemic symptoms. Finally, it should be mentioned that grand mal, petit mal, or Jacksonian epilepsy may result from apparently uncomplicated hypoglycemia. Usually, a careful history will reveal behavior preceding convulsions which would not be expected for idiopathic epilepsy.

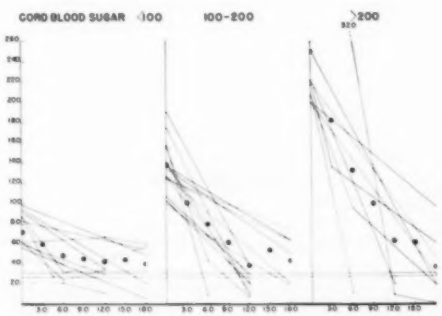


Fig. 1. Early fall of blood sugar in infants born of diabetic mothers, extent varying with the height of the blood sugar at birth.

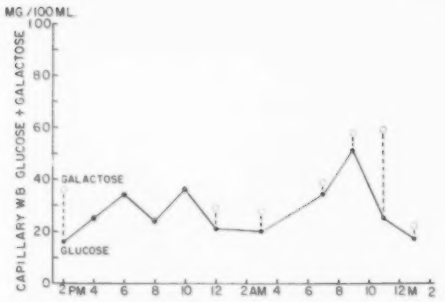


Fig. 2. The 24-hour blood sugar profile before treatment with ACTH of Donna W., in which all glucose values are abnormally low, and in which some galactose values are relatively high.

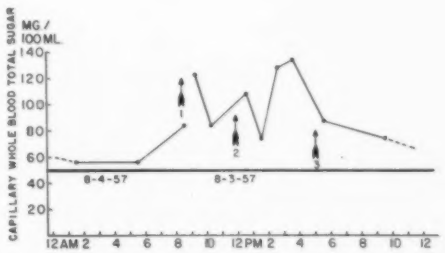


Fig. 3. The before-treatment, 24-hour blood sugar profile of Rose Marie Z., born July 14, 1955, in which no determination of true sugar is significantly low, and in which is suggested a definite, if slight, postprandial fall in blood concentration, probably attributable to the leucine content of 3 meals. Arrows *1*, *2*, and *3* represent meals.

The clinical pattern of hypoglycemia may vary considerably in different children, but each child is likely to have his own stereotyped pattern. In the case of Cecil R., which is referred to later, a typical episode of hypoglycemia was described as follows: Cecil was unusually quiet as his supper tray was brought to his bed, and he reacted scarcely at all to any sort of question or command, although his eyes were wide open. Orange juice with added sucrose was given orally with much coaxing. During part of the time of his feeding he seemed to understand what

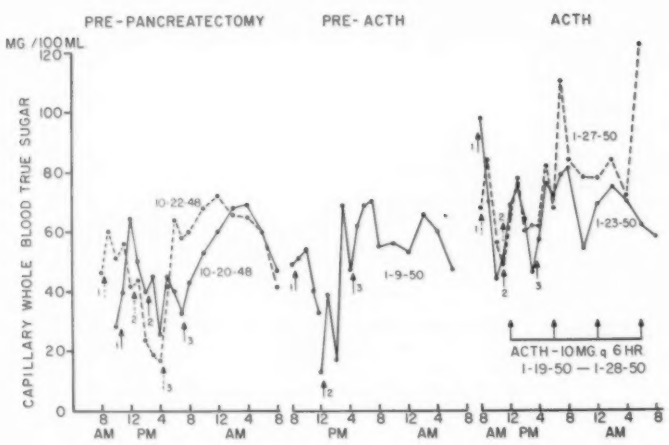


Fig. 4. Twenty-four-hour blood sugar profiles of Cecil R., before and during administration of ACTH, demonstrating the strong tendency of hypoglycemia to develop in midafternoon, and disappear at night and the significant hyperglycemic effect of the hormone.

was said but would then suddenly lose contact with the surroundings; his head would fall forward and hang limply on his chest, and consciousness would be lost completely for a few seconds, followed by quick recovery during which he would look about. Some 5 minutes after the orange juice feeding, his behavior was its usual "boisterous" one. His parents had noted that if many such minor episodes (petit mal) occurred at close intervals and were untreated with sugar administration, severe grand mal often followed. The hypoglycemic episodes of Donna W. were likewise stereotyped: Many would be ushered in with unusual sweating, a staring gaze modified often by a coarse nystagmoid movement of the eyeballs and twitching of the eyelids, coarse body and extremity tremors, and more or less continuous crying associated with prominent gasping inspirations. Following such an episode she could be anorexic, alternately irritable and listless, often sleeping for hours. In the case of Steven P., remarkably sensitive to leucine, an episode of severe hypoglycemia would often be heralded by a drooping of the right side of his mouth and unusual drowsiness, to be followed by a turning of the head and eyes to the left before the appearance of generalized tonic and clonic convulsive movements of all extremities. In the case of Randy S., whose hypoglycemia was the result of an islet cell adenoma, mischievous and often obstreperous behavior preceded attacks characterized by weakness, wabbling back and forth of the head, unusual cry, strabismus, either limpness or rigidity of the body, sweating, and finally unconsciousness.

Perhaps the best way, however, to be alert for the possibility of hypoglycemia, is to carry in the back of one's mind a simple clinical classification which would constantly be a reminder. Such a classification is presented in Table I.

In the attempted laboratory demonstration of hypoglycemia, there are a number of pitfalls that must be avoided. What must be demonstrated is *hypoglucemia*. It must be

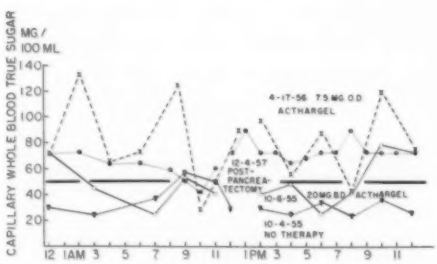


Fig. 5. Twenty-four-hour blood sugar profiles of Donna W., before and during ACTH administration and after pancreatectomy, demonstrating the effectiveness of corticotropin and subtotal pancreatectomy in raising the blood sugar to normal values.

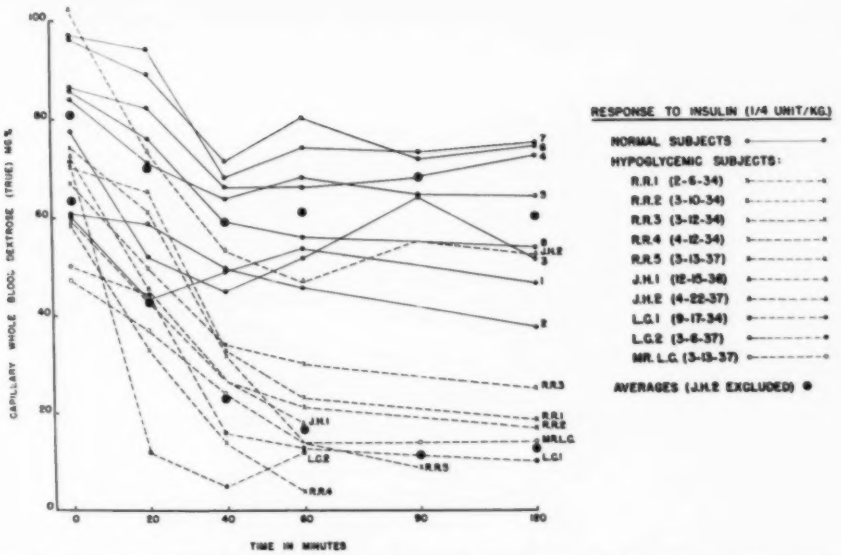


Fig. 6. The response of blood sugar of fasting normal (solid lines) and fasting insulin-sensitive hypoglycemia-prone children (dashed lines) to 0.25 units of insulin hydrochloride per kilogram of body weight. The response of an insulin-sensitive father (Mr. L. C.) of one child (L. C.) is also included.

remembered that methods for determination of blood sugar are still used in many hospitals which give false values. Thus a value as much as 30 mg. per 100 ml. above the true sugar level may be recorded. It usually makes a lot of difference if a value is zero, and not 25 or 30 mg. per 100 ml., as falsely indicated. In normal infants[4] the total true sugar concentration often includes galactose to the extent of 40 per cent, and in sick infants[5] sometimes all the sugar is galactose. Unless this sugar is converted to glucose, it is unavailable for brain cell metabolism and will not relieve the symptoms of hypoglucemia, although its undetected presence may seem to rule out the possibility. To avoid these two common pitfalls, we use the sensitive Shaffer-Hartmann-Somogyi method[5, 6] of true sugar determination, with and without removal of glucose by yeast fermentation.* Sometimes a postmortem low blood sugar value is regarded as uninterpretable and discarded. In this connection, it should be remembered that at 37° C. the average

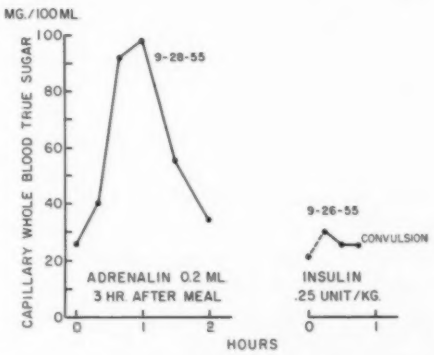


Fig. 7. Both the Adrenalin and the insulin tests confirm the tendency of the blood sugar to stabilize at a low level (Donna W.). The insulin test fails to demonstrate a condition of insulin sensitivity when the blood sugar is already low prior to administration of insulin.

*When such a semimicro method is used, however, one must be certain that contamination with exogenous glucose does not occur. If, for instance, the rubber stopper of the test tube containing the diluent for the small capillary blood sample is inadvertently placed on a spot on the bedside table where some 5 per cent glucose had been spilled (very easily done), enough glucose can be picked up to give a value of 700 mg. per 100 ml. when the real blood value might be zero.

Table I. Clinical classification of hypoglycemia

I.	Occurring in the neonatal period
	A. Due probably to transient hyperinsulinism plus increased sensitivity to insulin
	B. Due to islet cell hypertrophy and hyperplasia
	C. Due to adrenal destruction
	D. Due to intracranial injury
	E. Due to severe malnutrition
	F. Associated with actual or relative hypergalactosemia
	G. Associated with glycogen storage disease or other liver abnormality
	H. Associated with maternal toxemia of pregnancy
II.	Following discontinuation of extended parenteral glucose administration in the very young or malnourished child
III.	Recurrent and apparently caused by persistent sensitivity to insulin (sometimes referred to as "idiopathic," "spontaneous," "familial," etc.)
IV.	Persistent or very frequently recurrent and associated with insulin-secreting tumor, persistent marked insulin sensitivity, or sensitivity to leucine.

glycolytic rate of drawn blood is only 15 mg. per 100 ml. per hour; so a very low blood sugar determination taken a few minutes after death means that a very low one was also present during life. Also in this connection, some mention should be made of the value of the determination of spinal fluid sugar (both total and glucose). Quite commonly, the symptoms of a child in severe hypoglycemia are such that a lumbar puncture is indicated, and the unexpected finding of a low sugar concentration in otherwise normal spinal fluid has led to the prompt recognition of concomitant hypoglucemia. Conversely, the unexpected finding of a high sugar value in purulent spinal fluid has led to the diagnosis of concomitant hypergalactosemia[5, 7] of the congenital type, neither the patient's leukocytes nor the particular bacterium being capable of metabolizing galactose. Also in this connection, it should be remembered that glycolysis goes on very slowly in sterile spinal fluid which is free of cells, even at room temperature. Thus, one may secure an estimate of the blood-sugar concentration a few hours prior to the spinal tap from a spinal fluid sugar determination irrespective of whether the spinal fluid had been allowed to remain in the refrigerator or even at room temperature for some time.

When an episode of significant hypoglucemia has been identified the next task is to try to explain the pathologic mechanism, an understanding of which may be necessary for therapy and prognosis. Our routine workup at present is as follows.

1. Twenty-four-hour blood sugar profile. On a diet similar to the usual home one, and with sleep, rest, and activity also simulating the usual, hourly capillary whole blood true sugar determinations (C.W.B.T.S.) are obtained for a whole day. A 2-hour interval may suffice during the night. Such a profile immediately tends to screen out the persistent type from the occasional recurrent type. In the former many or all of the blood sugar levels will be abnormally low (Fig. 2), whereas in the latter none may be (Fig. 3) or perhaps only the ones at the end of the all-night fast may be a little low. Such a profile may also show a relationship of the hypoglycemia to eating, as might be expected in the leucine-sensitive type or in the type suspected to be due to true hyperinsulinism. It particularly may suggest a certain time of the day as the most critical one for the development of hypoglycemia (Fig. 4). It may also be of assistance in planning later tests with regard to timing and in the avoiding of spontaneous fluctuations of blood sugar which would make interpretation of tests difficult. Finally, it might be evidence of the effectiveness of treatment (Figs. 4 and 5).

2. Insulin tolerance test. Our second study is usually that of the response to insulin because, in our experience, the great majority of children have only occasional episodes of hypoglycemia and are found to be insulin sensitive and diagnosis by this test can be made at any time between hypoglycemic attacks, when apparently otherwise normal. We have found the dose, 0.25 units per kilogram of insulin hydrochloride,* the most

*For accurate administration of small doses, a tenfold dilution of U-40 insulin with physiologic saline solution is recommended.

useful single one, when given subcutaneously in lieu of breakfast after an all-night fast in the case of children 18 months or older or 4 to 6 hours after the last feeding in younger infants; blood sugar concentrations are determined at 0, 20, 40, 60, 90, 120, and 180 minutes. This dose seems necessary to rule out the mildest cases and should not be dangerous to the very sensitive ones, provided they are carefully observed and treated promptly and properly if hypoglycemic symptoms develop. The usual response in normal control children or in epileptics without hypoglycemic tendency is as described previously[5] and as pictured in Fig. 6. The fasting blood sugar is usually near 80 mg. per 100 ml., falls about 10 mg. during each of the first two 20 minute periods, and then tends to stabilize, sometimes rising a little, sometimes falling a little more, but remaining above 50 mg. per 100 ml. in all but the infants and very young children, where a fall to 40 mg. or so may occur, but always without clinical symptoms. The blood sugar of the insulin-sensitive child on the other hand, starting somewhat lower, tends to fall more rapidly and continues to fall beyond the 40-minute period. It very often falls to very low levels in 60 to 90 minutes and is accompanied by symptoms characteristic of spontaneous attacks. These are often severe enough to demand immediate discontinuation of the test and prompt restoration of a normal blood sugar level. Such insulin sensitivity may not always be demonstrated if the initial blood sugar is very low (Fig. 7). Apparently some insulin-sensitive children are capable of mobilizing considerable insulin opposition once the blood sugar becomes sufficiently low. This, however, is not always true, and sometimes a low blood sugar quickly drops to zero in response to insulin (Fig. 8). In the insulin-resistant type, such as our case with the islet cell adenoma (Fig. 12) and in a nontumor case (Fig. 9), before subtotal

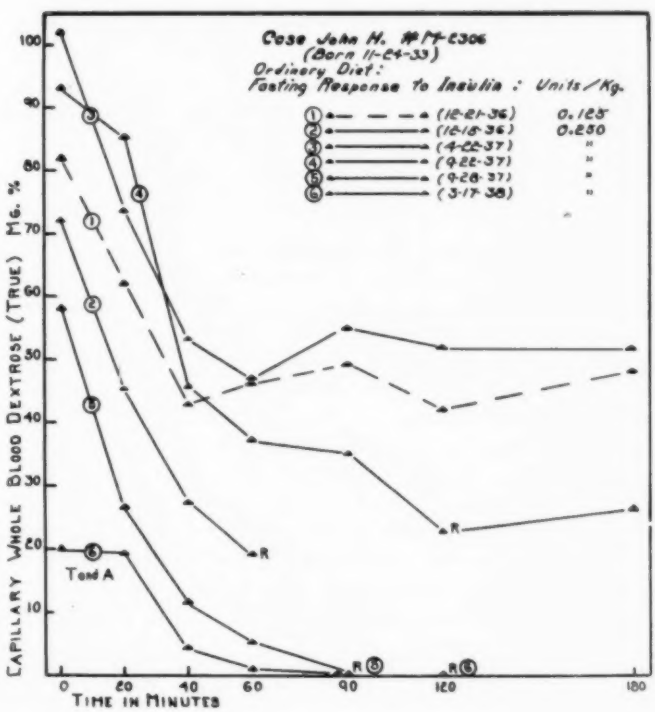


Fig. 8. Consistent insulin-sensitive responses to 0.25 units per kilogram insulin hydrochloride regardless of original fasting blood sugar level in recurrent hypoglycemia.

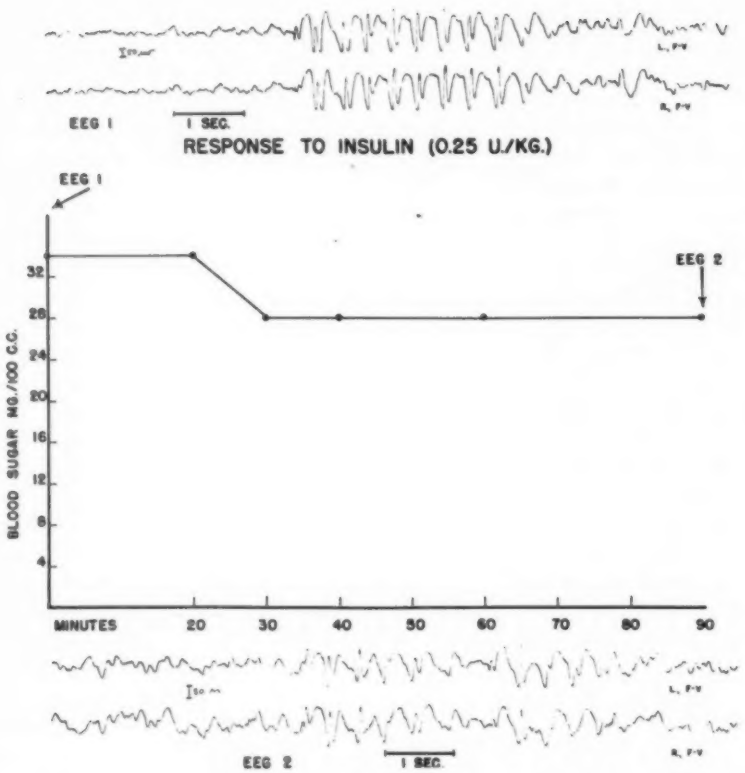


Fig. 9. Very little hypoglycemic response to insulin-sensitivity test (0.25 unit per kilogram) in Cecil R. with initially low fasting blood sugar who was thought to have hyperinsulinism due to excessive intake of sugar for a long period of time.

pancreatectomy, where hyperinsulinism was thought to have developed in response to excessive sugar feeding, there was little or no fall in response to insulin, and once even a rise.[9] In all our children receiving enough ACTH or adrenal steroid to control hypoglycemia, insulin responses tended to shift from sensitive to more resistant patterns, as pictured in Figs. 4 and 5. If, however, insulin is administered not in the fasting state but after the second meal of the day, the degree of hypoglycemia produced may fail to produce clinical manifestations (Fig. 10).

3. Glucose tolerance test. If the child eats lunch and supper well on the day of the insulin tolerance test, a standard glucose tolerance test may be performed the following day; if not, another day or two are allowed to elapse between tests. This policy is continued for the remaining tests. In lieu of breakfast after an all-night fast in children 18 months or older, or 4 to 6 hours after the last feeding in younger infants, 1.75 Gm. glucose per kilogram is fed in an appropriate amount of water, C.W.B.T.S. being taken at 0, ½, 1, 2, 3, and sometimes 4, 5, and 6 hours. With this test, one hopes to detect the subject who responds to glucose administration with hyperinsulinism, by noting some time during the 6-hour period, a marked insulin-caused drop in blood sugar, with appearance of hypoglucemic symptoms. In very marked contrast to the incidence in adults, apparently true hyperinsulinism is

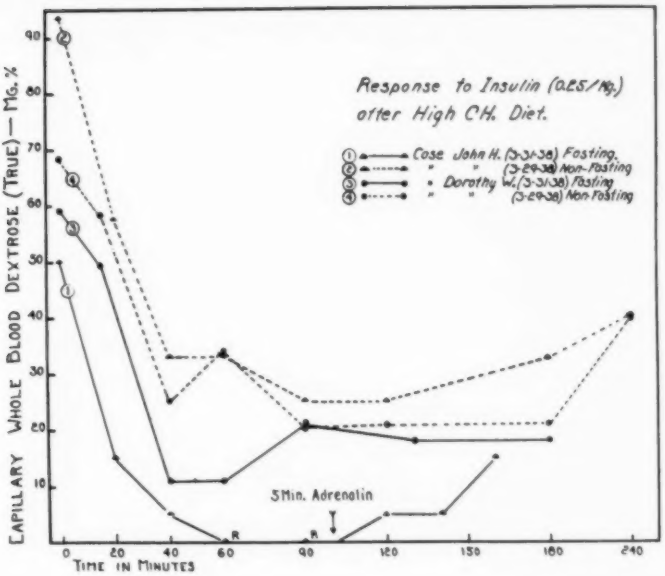

Response to Insulin (0.25/Kg.)
after High C.H. Diet.
Case John H. (3-31-38) Fasting.
" " (3-29-38) Non-Fasting
Dorothy W. (3-31-38) Fasting
" " (3-29-38) Non-Fasting
CAPILLARY WHOLE BLOOD DEXTROSE (TRUE) — MG. %
TIME IN MINUTES
5 Min. Adrenalin

Fig. 10. Demonstration of variation of fasting and nonfasting responses to insulin (0.25 unit per kilogram).

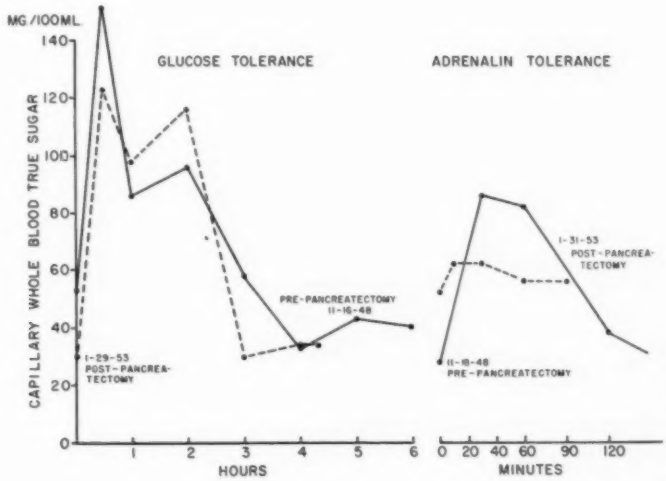


Fig. 11. Development of hypoglycemia during glucose tolerance test in Cecil R. thought to have hyperinsulinism due to excessive intake of sugar for a long period of time.

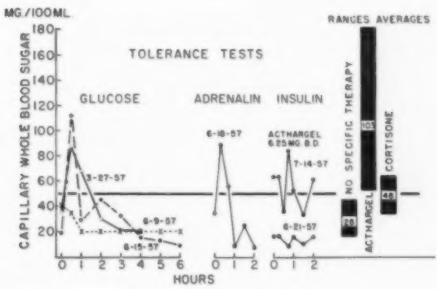


Fig. 12. Test responses of Randall S., born May 22, 1955, with insulin-secreting pancreatic adenoma. Note increase of hypoglycemia during the glucose and Adrenalin tests.

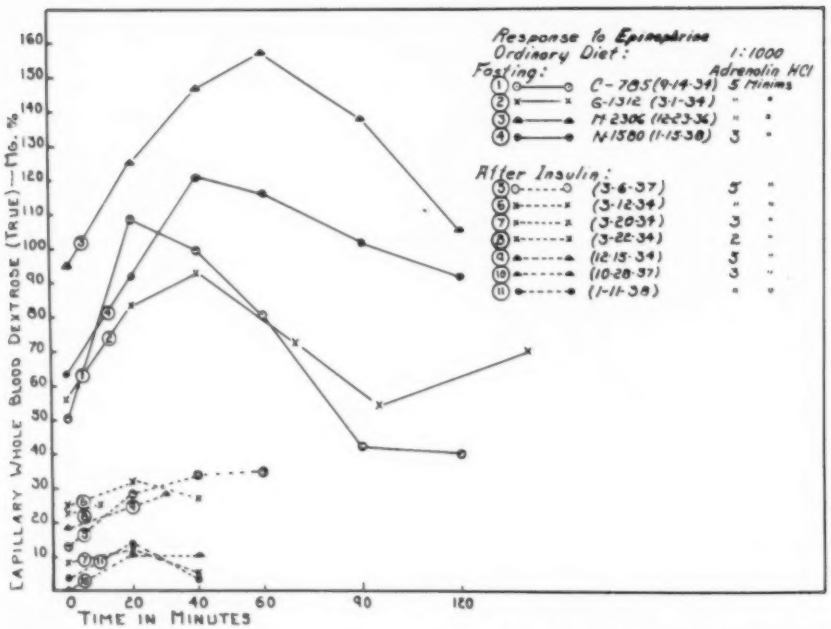


Fig. 13. Good glucogenic responses to epinephrine despite low fasting blood sugar concentrations; poor glucogenic responses in the same children while hypoglycemic from insulin administration.

very rare in children. Only 3 of our many patients with hypoglycemia on whom glucose tolerance tests were performed responded in this way: (1) Patient Cecil R. (Fig. 11), with presumptive iatrogenic hyperinsulinism before subtotal pancreatectomy, (2) Patient Randy S. before removal of the islet cell adenoma (Fig. 12) as contrasted with the normal response a few weeks after removal,[9] and (3) Patient Steven P.,[3] both insulin and leucine sensitive and still under observation with regard to possible hyperinsulinism.[9] The test's chief value has been to help establish whether or not fasting will tend to allow dangerous hypoglycemia to develop and, therefore, must be avoided and to indicate the level at which the blood sugar tends to stabilize postprandially and in the presence of glycogen stores. The finding of a low fasting blood sugar, with a return to the same low level after administration of glucose, cannot be taken as presumptive evidence of hyperinsulinism due to an islet cell adenoma. Such tumors are rare in infants and children; only 13 cases were reported in the world literature up to a few years ago.[10] Instead, such a response of the blood sugar is more apt to develop from a defect in glycogen storage or mobilization plus *relative* hyperinsulinism due to reduced insulin opposition. Such a mechanism seems to characterize most of the cases of recurrent insulin-sensitive

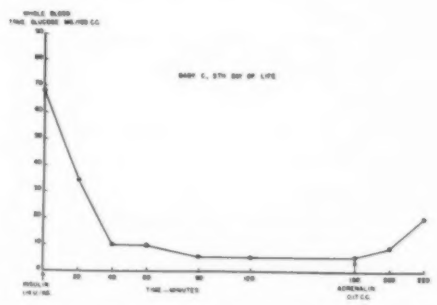


Fig. 14. Poor glucogenic response to epinephrine (Adrenalin hydrochloride 1:1,000 intramuscularly) in a normal newborn baby made hypoglycemic with insulin.

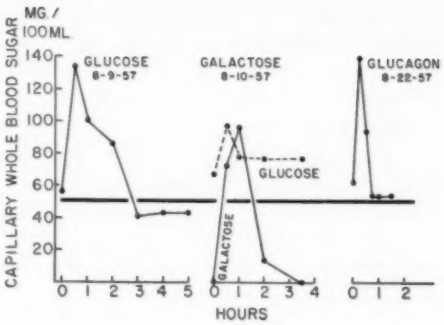


Fig. 15. Rapidly induced glucogenic response to glucagon intravenously in Rose Marie Z. with recurrent hypoglycemia.

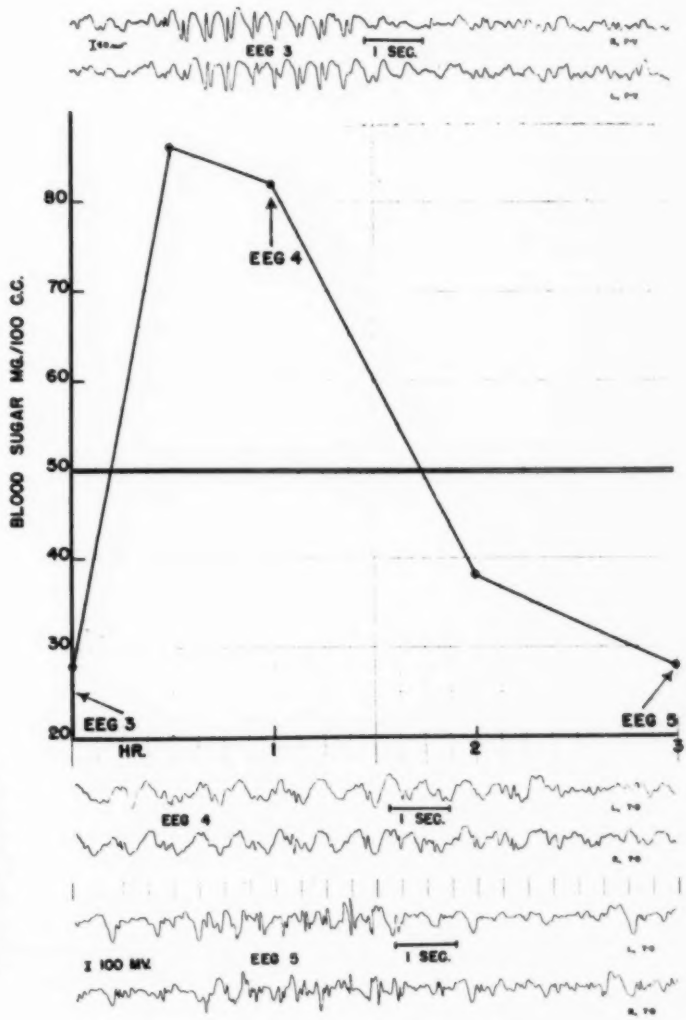


Fig. 16. Response to Adrenalin (0.2 c.c.) in Cecil R. Disappearance of dome-spike waves in the electroencephalogram during the rising phase of blood sugar after epinephrine and the reappearance of dysrhythmia coincidentally with recurrence of hypoglycemia.

hypoglycemia, sometimes referred to as "spontaneous idiopathic," "familial hypoglycemosis," etc., which as stated earlier constitute by far the most frequent type of hypoglycemia encountered in children.

4. Response to epinephrine. It is often helpful in planning therapy to establish whether or not glycogen stores in the muscles and liver are still present after an extended fast. A low fasting blood sugar cannot be interpreted to mean that there are no such glycogen stores. Despite a low fasting level, 0.1 to 0.3 ml., 1:1,000 aqueous Adrenalin intramuscularly may be followed by a significant increase in the blood sugar concentration (Fig. 13). Such a response is very common in the insulin-sensitive type of recurrent hypoglycemia. If, however, the low initial blood sugar level is the result of administration of insulin during the standard insulin tolerance test, many hypoglucemia-prone children, perhaps one half (Fig. 13), will not show a rise in blood sugar in response to Adrenalin, suggesting that adrenalin may not be a good form of emergency therapy for either spontaneous or insulin-induced hypoglycemia. It should be recalled[7] that a similar situation exists shortly after birth in normal infants (Fig. 14). Another way in which the response to Adrenalin has been helpful is the confirmation of the stabilized low level that tends to characterize a particular case. In Patient Randy S. (islet cell tumor, Fig. 12), the rise in blood sugar was followed by a fall to a very low level with severe clinical symptoms, as had happened following the administration of glucose, a response suggestive of hyperinsulinism. In the more severe von Gierke type of glycogen storage disease (due to absence or reduction in glucose-6-phosphatase), Adrenalin should fail to produce a significant rise in blood glucose.

5. Glucagon response. In a somewhat more rapid and decisive fashion, the administration of 20 mcg. per kilogram of glucagon provides information similar to that derived from Adrenalin, being, apparently, specific for liver glycogenolysis (Fig. 15). In one child, on one occasion, glucagon failed to stimulate a rise in blood glucose, apparently because of a temporary absence of liver glycogen, secondary to fasting and illness. Later, after normal eating, a good rise in blood glucose followed administration of glucagon. Blood sampling should be at 0, 10, 20, 40, 60, and 90 minutes. Our over-all experience with glucagon is not sufficient to allow us to state a preference for it over Adrenalin, either as a test substance or a therapeutic agent. On the contrary, because of its ready availability, low cost, and ease of administration even by parents, Adrenalin perhaps is to be preferred.

6. Leucine response. The now common knowledge that some children are remarkably sensitive to some of the amino acids such as l-leucine, makes it imperative that the response to leucine be observed in all children suspected of having a tendency to hypoglycemia. Our first 2 leucine-sensitive children were also insulin sensitive,[9] as have been 2 subsequent patients, not reported upon. One, Patient Steven P., reacted strikingly to one fifteenth of the suggested test dose of l-leucine of 0.15 Gm. per kilogram. What the best screening dose will be still remains to be decided. It does seem, however, because of the speed with which l-leucine produces hypoglycemia, that it should be given intravenously, so that vomiting and variability of absorption from the gastrointestinal tract can be avoided, as well as the necessity of giving it otherwise by gavage, because of its obnoxious taste. For this purpose a 1.67 per cent solution adjusted to pH 7.4 with sodium hydroxide and sterilized by autoclaving, seems satisfactory. Blood sampling should be at 0, 5, 10, 15, 30, 45, and 60 minutes.

7. Galactose response. As mentioned before, the interpretation of a blood sugar value may require separation of galactose from glucose. This is particularly true in young infants whose diet is largely milk (Fig. 1) and in the children with a disturbance of galactose metabolism.[5] In the latter, hypoglucemia may exist in the presence of a normal or elevated total sugar, which, of course, is largely galactose. In such

children, administration of galactose with resulting hypergalactosemia may be followed by hypoglucemia. In the von Gierke type of glycogen storage disease, even though the metabolism of galactose is normal, its administration theoretically should not be followed by a rise in blood glucose because of absence of liver glucose-6-phosphatase. The dosage of galactose used in the study of such cases is usually 1.75 Gm. per kilogram with the blood sampling intervals being the same as in the glucose tolerance test.

8. Encephalography. It has frequently been helpful to include electroencephalography in the study of children with seizures suspected of having a strong hypoglycemic component. Generally the electroencephalogram has been obtained before, during, and after a test likely to produce significant changes in blood glucose concentration. Our over-all experience with such studies will be the subject of a later paper. It should be of interest at this time, however, to include the results of one such study of Cecil R. (Fig. 16).

9. Blood insulin assay. The biologic test of insulin stimulation of carbon dioxide production in the rat epididymal fat pad[11] can be used as a nonspecific method of insulin assay and may serve in the future to clarify further the mechanisms of some types of hypoglycemia. Of still greater value should be a specific measure of insulin concentration such as by the insulin antibody technique.[12] Findings in hypoglycemic children with such methods have already been recorded.[13, 14] Our own findings will be the subject of a future report.

REFERENCES

1. Pennoyer, Miriam M., and Hartmann, A. F.: Management of Infants Born of Diabetic Mothers, Postgrad. Med. **18:** 199, 1955.
2. Geiger, Alexander: Correlation of Brain Metabolism and Function by Use of a Brain Perfusion Method in Situ, Physiol. Rev. **38:** 1, 1958.
3. Koerner, Kenneth A.: Congenital Goiter With Exophthalmos and Hyperthyroidism, J. PEDIAT. **45:** 464, 1954.
4. Hartmann, A. F., Grunwaldt, Edgar, and James, David H.: Blood Galactose in Infants and Children, J. PEDIAT. **43:** 1, 1953.
5. Hartmann, A. F., McCoy, Ernest E., Swarm, Pauline A., and Nakasato, Doris I.: Further Observations on the Metabolism of Galactose in Infants and Children, J. PEDIAT. **44:** 499, 1954.
6. Somoygi, M.: A Reagent for the Copper-Iodometric Determination of Very Small Amounts of Sugar, J. Biol. Chem. **177:** 777, 1937.
7. Hartmann, A. F.: Pathologic Physiology in Some Disturbances of Carbohydrate Metabolism, J. PEDIAT. **47:** 537, 1955.
8. Hartmann, A. F., and Jaudon, Joseph C.: Hypoglycemia, J. PEDIAT. **11:** 1, 1937.
9. Hartmann, A. F., Sr., Wohltmann, H. J., Holowach, J., and Caldwell, B. M.: Studies in Hypoglycemia, J. PEDIAT. **56:** 211, 1960.
10. van Beek, C.: Spontaneous Hypoglycemia and Hyperinsulinism in Infants and Children, Maandschr. kindergeneesk. **20:** 141, 1952.
11. Penold, Albert E., Martin, Donald B., Dagenais, Yves M., Steinke, Jurgen, Nickerson, Rita J., and Sheps, Mindel C.: Measurement of Small Quantities of Insulin-Like Activity Using Rat Adipose Tissue, J. Clin. Invest. **39:** 1487, 1960.
12. Yalow, R. S., and Berson, S. A.: Assay of Plasma Insulin in Human Subjects by Immunological Methods, Nature **184:** 1648, 1959.
13. Grumbach, Melvin M., and Kaplan, Selna L.: Amino Acid and Alpha-Keto Acid-Induced Hyperinsulinism in the Leucine-Sensitive Type of Infantile and Childhood Hypoglycemia, J. PEDIAT. **57:** 346, 1960.
14. Mabry, C. Charlton, DiGeorge, Angelo M., and Auerbach, Victor H.: Leucine-Induced Hypoglycemia, J. PEDIAT. **57:** 539, 1960.

CLINICAL PATHOLOGICAL CONFERENCE

THE CHILDREN'S HOSPITAL MEDICAL CENTER, BOSTON, MASS.

Sidney Farber, M.D., Editor
Gordon F. Vawter, M.D., Assistant Editor

THIS 18-month-old Negro female was well until two weeks before admission when she developed coryza and cough without fever. The cough was described as of a barking nature. Nothing is known regarding paroxysm and inspiratory whoops. Four weeks before the patient's admission, her siblings, aged 7, 5, and 4 years, began to have coughing, diagnosed as pertussis. None of the children had been immunized with diphtheria-pertussis-tetanus vaccine. Five days before admission, the patient's cough became more severe and some respiratory distress was noted. One night before, the patient was noted to be febrile and an apneic period occurred, lasting about 10 seconds, from which she was resuscitated by her father after mouth-to-mouth breathing. Four hours after admission to another hospital, the patient had a period of cardiac arrest lasting 4 minutes. One cubic centimeter of adrenalin was injected into the heart and beating resumed. X-ray of the chest showed pneumonia in the right middle lobe. The white blood count was 74,000 per cubic millimeter, with 65 per cent lymphocytes. Lumbar puncture showed opening pressure 105 mm. saline, closing pressure 65 mm. saline, cells 0, protein 24 mg. per cent, and sugar 68 mg. per cent. She received 1,000,000 units of penicillin intravenously every 4 hours and 100 mg. streptomycin every 4 hours intramuscularly and on the following night was given 25 mg. Thorazine by suppository and 65 mg. of intravenous phenobarbital. She was then transferred to The Children's Hospital Medical Center.

Past history revealed hospitalization for pneumonia at the age of 4 months. Physical examination disclosed temperature 98.6° F.; pulse rate 160 beats per minute; blood pressure 96/60 mm. Hg; respirations 52 per minute. The child was acutely ill with severe respiratory distress, evidenced by grunting, intercostal retractions, and flaring alae nasi. She was markedly irritable with thrashing about and twisting movements. A purulent blood-streaked nasal discharge was noted. The pharynx was injected. The trachea was thought to be slightly shifted to the right. The anteroposterior diameter of the chest was increased with hyperresonance present bilaterally, greater on the left than on the right. The edge of the liver was 3 cm. below the costal margin and the tip of the spleen was felt. There was no adenopathy,

except small shotty nodes. Generally scattered fine râles were heard both anteriorly and posteriorly on the right. Neurological examination showed hypotonia with hyperactive reflexes. Chest film revealed a left tension pneumothorax with all but complete collapse of the lung. Heart and mediastinal shadows showed a minimal shift to the right. The right lung was irregularly ventilated, somewhat increased in volume, and showed extensive peribronchial inflammatory reaction consistent with pneumonia and atelectasis of the major portion of the middle lobe.

Attempts were made to remove the air from the left hemithorax by needle and syringe, with both anterior and posterior approaches. The former yielded 5 c.c. of air, and the latter 90 c.c. X-ray showed no change following these procedures. While surgical consultants were preparing to place a chest tube in the left thorax, the patient developed sudden cyanosis, became opisthotonic and apneic. An endotracheal tube was passed, and this assisted respirations and maintained ventilation of the right lung. This was followed by a cardiac arrest 4 minutes later. Intracardiac adrenalin was given, followed by a thoracotomy and cardiac massage for 40 minutes. Respirations and heart beat did not resume.

Nose culture gave no growth. Throat culture grew few *Escherichia coli*. The Bordet-Gengou culture of the throat was negative. The white blood cell count was 79,100 per cubic millimeter, with 80 per cent lymphocytes and 20 per cent polymorphonuclear leukocytes.

DR. R. CANNON ELEY.* One cannot help, even after the most cursory analysis, but make a diagnosis of whooping cough in this case. The illness occurred after a 2-week incubation period in March, season of maximum morbidity, in a girl at the very susceptible age of 18 months, the maximum incidence (48 per cent) of cases occurring before the age of 4 years, with 4.5 per cent occurring before 1 year of age. There were 796 cases of pertussis tabulated in Massachusetts in 1959 whereas, so far, in 1960 we have an unusually fine record with only 188 instances noted. As a matter of fact this past July was the first time since whooping cough became a reportable disease in this state that a 2-week period passed without a single reported case. This suggests the benefits derived from our current immunization procedures. Also the cough, as described, does not sound as it were croupy, and the lack of fever is against the diagnosis of bronchitis or other usual respiratory infection. Nor was there a brassy cough as seen with foreign body or other intrinsic laryngeal lesion. So I am content with a diagnosis of pertussis on clinical grounds. The negative culture for pertussis organisms does not particularly bother me; some laboratories are notorious for the percentage of negative cultures, whereas others are notorious for the number of positive cultures.

It is interesting to learn that about 90 per cent of children entering the first grade in Massachusetts schools have been immunized against pertussis, but here we have a family of 4 children, none of whom had been immunized.

Now, 5 days before admission respiratory symptoms were noted and so perhaps we are not surprised that apnea occurred. A prolonged bronchiospasm and build up of carbon dioxide following a paroxysm of coughing can easily lead to such apnea. The tempo of her illness increased, so that while in another hospital cardiac arrest occurred, which, I should suppose, most likely was mediated through a vagal mechanism. A rather generous dose of Adrenalin restored the heartbeat. I should have thought that one half of this dose, or less, would have served. We are faced, too, with considerable leukocytosis or better, lymphocytosis, and we wonder what the hemoglobin and platelet values were.

DR. DAVID H. CARVER. These values are not available.

DR. ELEY. A lumbar puncture revealed normal cerebrospinal fluid. I suspect it was

*Dr. R. Cannon Eley is Physician and Director of Postgraduate Education at The Children's Hospital Medical Center, Boston, and Assistant Clinical Professor of Pediatrics at Harvard Medical School.

done so as not to overlook meningitis or other process, rather than with any great expectation of finding an abnormality. The antibiotic treatment given seems pretty heroic, unless one suspected bacterial endocarditis, and probably this was begun before the lymphocytosis was discovered since ordinary pyogenic infections seem unlikely in the face of such response. Next we wonder why she was given tranquilizers and sedatives. Later we learn that she was markedly overactive, and one wonders whether she was having convulsions or whether she was behaving irrationally. With a bloody and purulent nasal discharge, one should attempt to exclude diphtheria but, actually, epistaxis is not uncommon in pertussis. Physical examination on admission suggests that a degree of pneumothorax was already present as confirmed later by x-ray. The neurological examination could fit with sedation, early collapse, or both.

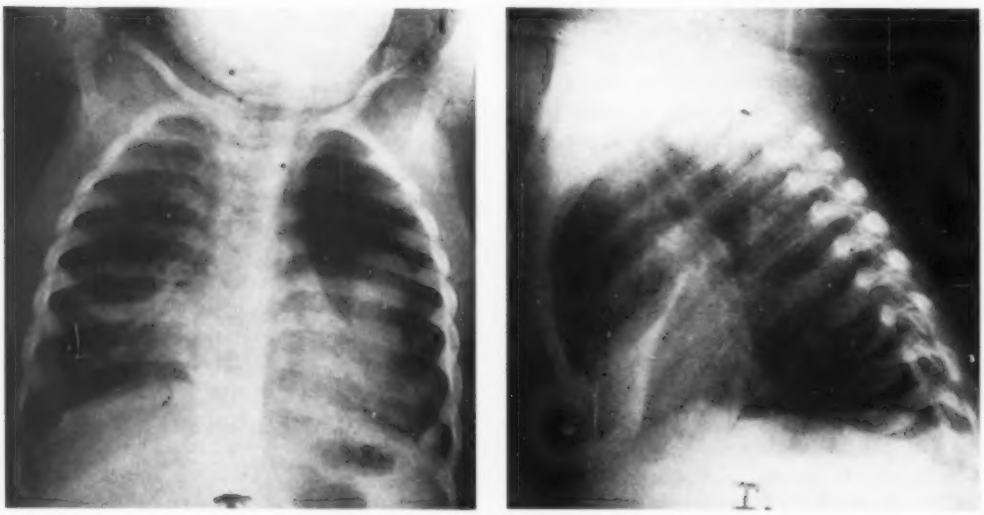
Perhaps we could see the x-rays.

DR. E. B. D. NEUHAUSER. There is a left-sided tension pneumothorax with nearly complete collapse of the lung and mediastinal shift to the right. On the right there is peribronchial infiltration which is consistent with pneumonia and atelectasis, especially of the middle lobe. The cardiac shadow is enlarged, as well.

DR. ELEY. Thoracentesis did not prevent the terminal episode of opisthotonos and apnea, which I suspect is central in origin, due perhaps to cerebellar or medullary compression. Cardiac arrest followed, despite endotracheal intubation. I cannot distinguish between central or vagal origin for this final event.

Now I have said that one can only make a diagnosis of pertussis in this instance. We can give some passing thought to acute leukemia and infectious mononucleosis, although confirmatory data are not here recorded. On the other hand, I have seen leukocyte counts of up to 240,000 per cubic millimeter in pertussis, and lymphocytosis is the rule. More than once I have seen an erroneous diagnosis of leukemia in pertussis. Dr. W. L. Bradford has pointed out the great difficulties in distinguishing pertussis from parapertussis unless one has definitive bacteriologic studies.

Pneumonia, pneumothorax (from rupture



A *B*

Fig. 1. *A* and *B*. Postanterior and lateral x-rays of chest, showing left pneumothorax and hyperaeration, streaky densities, and middle lobe consolidation on the right.

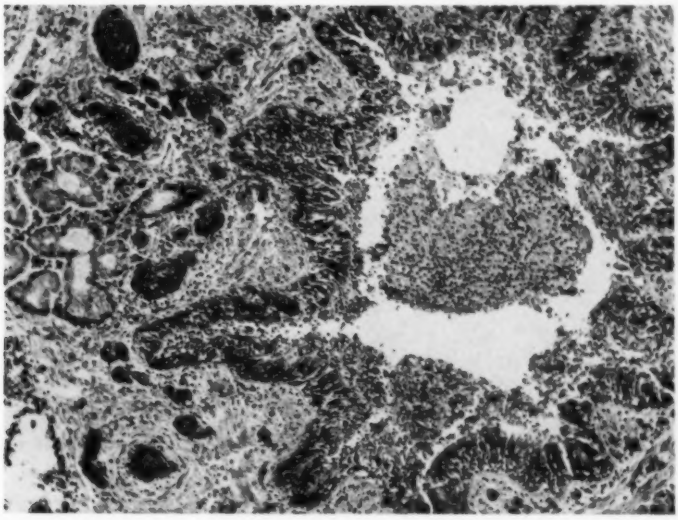


Fig. 2. Medium-sized bronchus showing luminal exudate and leukocytic infiltration at base of bronchial epithelial cells, with preservation of surface structure, as described in pertussis. (Hematoxylin and eosin. Original magnification ×125.)

of the lung during a paroxysm perhaps), epistaxis, encephalitic signs (possibly due to massive bleeding or to petechial hemorrhage or to encephalitis) are all well-known complications of pertussis. These latter can lead to the well-known late sequelae of pertussis in the central nervous system, such as encapsulated hemorrhage, healed encephalopathy, sometimes with hydrocephalus ex vacuo or cerebral atrophy, and so on. One of the worst examples of these complications was in a child who on admission was blind, was an idiot, and quadriplegic, all in one, following pertussis.

One of the best ways to treat this kind of situation is to prevent it. The vaccines used in this state seem to be doing the job very well, but the July 25, 1960, issue of the weekly publication of the Massachusetts Department of Public Health expressed concern over the fact that the antipertussis components of 5 out of 6 lots of commercial quadruple vaccine (pertussis, diphtheria, tetanus, and polio) failed badly as far as the pertussis antigen was concerned. One such commercial product has been withdrawn from the market. Other sources have been concerned, as well.*

DR. JOHN A. V. DAVIES. When I was in charge of the Bacteriology Laboratories, we had as much difficulty in culturing *Hemophilus pertussis* as there seems to be now. As Dr. Eley has suggested, it is a discouraging matter. Recently it has been proposed that the fluorescent antibody technique which has been applied to other bacteriologic problems, such as streptococcal typing, be developed and used for diagnostic purposes in pertussis. Relatively speaking, we see so few cases of whooping cough now that it is easy to overlook the diagnosis, especially when it is difficult to establish it, bacteriologically. As far as quadruple vaccination is concerned, I have preferred to mix the triple vaccine and the polio vaccine fresh each time, and I believe that this is no disservice to the patient.

Dr. Sydney Gellis has just raised the question of the encephalitic picture in this

*A current problem in immunization, Editorial, New England J. Med. 263: 656, 1960.

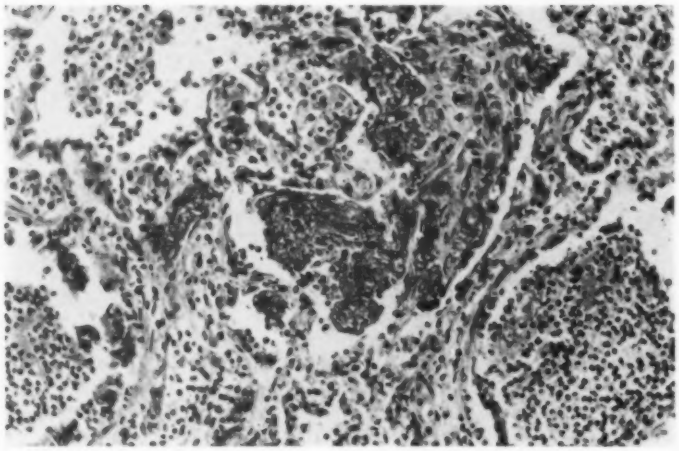


Fig. 3. Organizing bronchiolitis. Note the scattered large dark nuclei. (Hematoxylin and eosin. Original magnification ×250.)

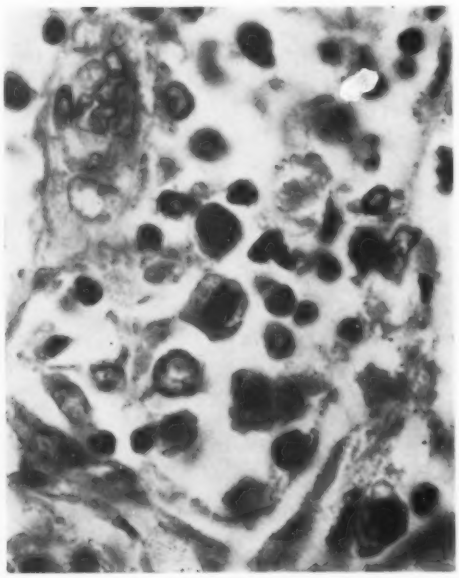


Fig. 4. Peribronchial lymph node with nuclear changes of adenovirus infection. Note the black (basophilic) barlike intranuclear structure surrounded by pallid nuclear material containing pale (eosinophilic) crystals. Below is an eosinophilic intranuclear body and above is a homogenized hyperchromatic nucleus. (Hematoxylin and eosin. Original magnification ×375.)

case. This reminds me of the time when we were somewhat reluctant to use pertussis vaccine because of encephalitic complications which sometimes followed its use. With the preparations we now use we see very little of this complication and even the postvaccination febrile responses have been largely eliminated much to the credit of our own State Biological Laboratories and Drs. James Coombs and Johannes Ibsen.

Dr. Eley. As far as encephalitis is concerned, the studies carried out by Dr. Tom Rivers and others on postvaccination encephalitis all seem to indicate that the incidence of this complication increases if the immunization is carried out after 2 years of age, this being more important, apparently, than the difference in the immunizing agents used.

Dr. Sidney Farber. Dr. Janeway, would you like to comment on this?

Dr. Charles A. Janeway. I am just an old-fashioned physician who does not believe that every symptom has to be treated. One wonders whether the use of tranquilizers is justified in this case, especially when one remembers the paradoxically hypertonic and hyperactive states which may rarely follow use of Compazine, for instance.

Dr. Gordon F. Vawter. The heart weighed half again as much as normal with left ventricular hypertrophy, possibly related to anemia or prolonged infection. One of

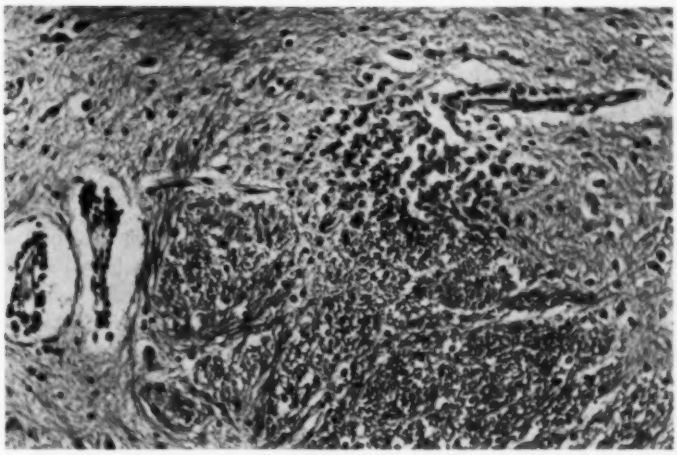


Fig. 5. Perivascular cuffing is seen on the left in this section of medulla. (Hematoxylin and eosin. Original magnification ×250.)

the most pronounced gross abnormalities was the dilatation and flabby character of the right ventricle. While there was mild hepatic congestion, most of the clinically apparent hepatic enlargement appeared to result from emphysema and downward thrust of the diaphragm. The adrenal glands were also half again normal in weight. While the brain was somewhat underweight, there were evidences of injury antedating the current illness. Two acute lesions involving the central nervous system were present microscopically which were not recognized grossly. One of these was a quite definite leptomeningeal polymorphonuclear leukocyte response indicating an acute meningitis either very early or quite mild. The other was distinct perivascular cuffing by round cells found only in the medullary area, indicating an encephalitic component. No hemorrhagic manifestations were demonstrated in the brain.

Only a small amount of bubbly mucoid material was found in the relatively unremarkable upper respiratory tract but microscopically there was a rather mild (by comparison with smaller bronchi) lymphoid and mononuclear cell infiltration in the submucosa. Large dark nuclei are formed here and in the regenerative surface epithelium; possibly these last are senescent forms resulting from viral parasitism.

Grossly the pale pink right lung was hyperaerated except for reddish consolidation in the middle lobe. In interlobar septae especially, one could see the distended gas-filled blebs of interstitial emphysema. The left upper lobe was also hyperaerated while the lower lobe was almost completely atelectatic. Interstitial emphysema was present in this lung also, as well as in the mediastinum as predicted in the x-ray.

Microscopically, purulent exudate fills most bronchial lumina, inflammatory cells infiltrate the bronchial submucosa and deep parts of the mucosa, but superficial cells and cilia are often left intact. This pattern of involvement has been considered typical in pertussis. Chronic pneumonitis, with epithelial regeneration, bronchiolitis being organized by fibroblastic proliferation, and areas of acute pneumonia were present, particularly in the right middle lobe. Here and there one notes the large, dark, nuclear masses which resemble those in tracheal epithelium. Again these are very likely the late stages of the effects of viral parasitism which was identified, especially in hyperplastic peribronchial lymph nodes. In the latter area there are large irregular cells with enlarged nuclei, containing the pale almost colorless, reddish intranuclear crystalline masses and the rosette or flowerlike bluish purple masses seen in adenovirus Type VII infection. The clinical picture of progressive respiratory disease, the virologic isolation of an adenovirus, and the histopathology of

the lesion have been extensively reviewed by a group in Paris.[1] This raises a point of some interest, in relation to the peculiar biology of infections with these viruses, in that desoxyribonucleic acid is involved, whereas many viruses such as herpes, measles, and so on, prominently involve ribonucleic acid synthesis. The biochemical, cytochemical, and morphologic aspects of this have been studied further by Dr. Leuchtenberger,[2] who has seen the slides in this case and concurs with the diagnosis. This study indicates a regular sequence of intranuclear changes varying with time after infection. This case, clinically, fits well with the prolonged respiratory illness described in instances of such infection, but one should emphasize that these cellular alterations differ from the viral inclusions described in up to 40 per cent of fatal cases of whooping cough in St. Louis; these latter appear largely to have been ribonucleic acid viral infections. The bone marrow of this patient is very active with a myeloid left shift and an increase in large dark cells resembling plasma cells or atypical lymphocytes in some respects.

Bacteriologic cultures of trachea, lung, and heart blood grew only *Escherichia coli.* If *H. pertussis* were present (organisms of this type were not recognized in the sections) it is not surprising that it was not cultured in view of the antibiotic treatment and of the presence of *E. coli,* which is believed to reduce the likelihood of successful culture.

In summary, we have a patient with an illness resembling *whooping cough* both clinically and pathologically, in whom evidences of an *adenovirus* infection were recognized.

REFERENCES

1. Chany, C., Lepine, P., Lelong, M., Le-Tan-Vinh, Satgè, P., and Virat, J.: Severe and Fatal Pneumonia in Infants and Young Children Associated With Adenovirous Infections, Am. J. Hygiene **67:** 367, 1958.
2. Boyer, G. S., Leuchtenberger, C., and Ginsberg, H. S.: Cytological and Cytochemical Studies of HeLa Cells Infected With Adenovirus, J. Exper. Med. **103:** 195, 1957.

COMMENTS ON CURRENT LITERATURE

Diarrhea caused by deficiency of sugar-splitting enzymes

THE possible causes of chronic and recurrent diarrhea in infants and young children are numerous. Exclusive of the infectious and parasitic types, etiological considerations must include allergy to ingested food; overuse of rough or irritating food; nutritional deficiencies and poor nutritional status; defective digestion, as in pancreatogenous steatorrhea; defective absorption, as in chronic idiopathic steatorrhea or other forms of celiac disturbance; and intrinsic disease such as neoplasms, or extrinsic influences of an endocrinopathic nature, such as thyroid disturbance.

The pediatrician is sometimes confronted in day-to-day practice with diarrheal conditions for which no cause can be found. In this connection a recent report from the Wilhelmina Children's Hospital in Utrecht, Holland, is of interest. This report by Weijers and his associates[1] appears in the *Acta paediatrica* for January, 1961, and concerns diarrhea caused by a deficiency of sugar-splitting enzymes. Three children with this condition were studied in detail by these authors. The first was a girl 14 months of age at the time of hospital admission. An inquiry into this child's previous history disclosed that she was the first born of healthy parents, with delivery at term considered normal in every respect. The birth weight was listed as 3,500 grams. After one week of breast feeding, Lactogen feedings were initiated. This formula was well tolerated, and defecation was normal. The child thrived and grew well for the first 5 months of life. When she was about 5½ months of age, the infant became ill with sudden onset of fever and diarrhea. On the second day of illness the temperature returned to normal, but the diarrhea persisted in spite of therapeutic measures. These measures included antibiotics, control of dehydration, and maintenance of electrolyte balance, Arobon (a carob powder), buttermilk, protein milk, wheat-free diet, and the like. Her weight gain which had been normal for 5 months was arrested.

On admission to the hospital at the age of 14 months, the child was dystrophic with a weight of 9,900 grams, and a height of 80 centimeters. Muscular development appeared to be normal for her age. The child was extremely irritable, petulant, and somewhat negativistic. Physical examination was essentially normal except for a flaccid swollen abdomen. Lively intestinal sounds were heard on auscultation. A profuse diarrhea was present, characterized by thin, foamy, voluminous stools containing much fine mucus. In the course of the hospital stay the following conditions were eliminated as causes of the diarrhea: such enteric infections as bacillary dysentery, typhoid, and paratyphoid fevers and infections by various enteric coli or by other pathogenic intestinal flora; amebic dysentery; giardiasis, parasitic worms; celiac disease, pancreatic fibrosis; anatomic anomalies of the gastrointestinal tract, terminal ileitis; latent iron deficiency, and vitamin deficiencies. Congenital alkalosis, milk allergy, and ganglioneuroma, likewise, were discarded as possible causative factors.

The second case was that of a male child, 2 years of age at the time of hospital admission. He was the second-born child of healthy parents. Born one month prematurely, (birth weight 2,300 grams), but delivered normally, this child did well on breast feeding for the first 6 months of life, with no diarrhea; his weight at this time was 6,500 grams. Shortly after the sixth month, persistent diarrhea began with thin, yellow, foamy stools 2 or 3 times daily. At the time of admission the child still suffered from recurrent chronic diarrhea. Physical examination at this time revealed a moderately well child who was reasonably active, but extremely pale, with abdominal distention and general hypertonia. During the periods of more severe diarrhea the child was fretful and whimpering, and often unruly. Improvement in the diarrhea was noted following the feeding of a protein milk/water/glucose mixture. With this improvement in the diarrheal condition, the child's disposition improved. Weight on hospital admission was 9,800 grams; height was 77 centimeters. All known causes for the diarrhea were ruled out by careful studies conducted during the hospital stay. Attempts at diet control appeared to be the only successful approach to therapy.

The third child was a boy born at term with normal delivery; the birth weight was 4,300 grams. He was breast fed for a few days only; diarrhea in this child became a problem after the first few weeks of life. Diets consisting of half milk/half water, of buttermilk mixtures, or of whole milk mixtures were not satisfactory. Normal stools were produced only when the diet consisted of a protein milk/water/glucose mixture. The diarrhea was characterized by foamy water-thin stools containing fine mucus. On admission to the hospital at the age of 1 year, the child was pale and fretful. Weight at this time was 8,700 grams, and height 75 centimeters. Examination on admission failed to reveal any abnormal physical signs, apart from a flaccid swollen abdomen. The patient was the fourth child of healthy parents. Two intermediate siblings have always enjoyed good health, but the eldest child, 13 years of age, has suffered all her life from a mild chronic recurrent diarrhea, necessitating restricted diet which had been arrived at empirically.

Since the diarrhea observed in all 3 of these patients was characterized by thin, foamy, often bulky stools containing fine mucus, considered typical of diarrhea originating in the small intestine, the authors gave some thought to an absorption disturbance as the causative factor. The characteristic foaminess and the low pH of the feces suggested the possibility of a disturbance in carbohydrate absorption. The authors point out that under these circumstances the nutritional components to be suspected are starch, lactose, and saccharose, since these substances cannot pass the intestinal wall as such, in contrast to the monosaccharides, glucose, galactose, and fructose, which can be absorbed. Normally starch, lactose, and saccharose are split in the intestine into monosaccharides, glucose, glucose + galactose and glucose + fructose, respectively, before absorption takes place. If the carbohydrate-splitting enzymes, amylase (diastase), maltase, lactase, and invertase (saccharase), are absent or insufficiently active, starch (dextrins, maltose), lactose, and saccharose may reach the ileocecal region intact. Here they are subject to intestinal bacteria and may undergo vigorous fermentation resulting in the formation of lower organic acids with the characteristic distressing consequences to the patient. A careful study of these 3 patients was stimulated to some extent by a report in 1959 by Holzel, Schwarz, and Sutcliffe[2] in which they describe 2 children in the same family with chronic diarrhea and malnutrition due to a lactase deficiency. Lactosuria was not a cardinal feature of the condition.

In the study by Weijers and his coworkers,[1] carbohydrate tolerance tests, examination of feces, and detailed enzyme studies were carried out on all 3 patients. These results are given by the authors in graphic and tabular form, with specific laboratory methods described in the ad-

denda. All 3 children were found to be suffering from enzyme deficiencies, maltase, and/or invertase. Only traces of sugar were excreted in the urine. One of the 3 patients could convert neither maltose (also starch) nor saccharose into monosaccharides, while the other 2, although capable of converting starch into glucose, were incapable of splitting saccharose into glucose + fructose. Consequently, in all these children the nonabsorbed disaccharides and starch are subject to attack by bacteria farther down in the intestine, with resultant fermentation and formation of organic acids, mainly lactic and acetic acids. Volatile lower fatty acids which occur under these circumstances can be differentiated by chromatographic methods. Irritation, increased peristalsis, excretion of fluid, and mucus formation are the result, followed by disturbed absorption and diarrhea. Invertase deficiency alone could be compensated for by the use of an invertase preparation, or by a strict saccharose-free diet. The maltase deficiency could not be compensated by the maltase and glucosidase preparations available. The authors suggest that the problem of therapy, which is currently under investigation, may be solved by the use of combined enzyme preparations, enteric coated, so that the maltase is not inactivated in the stomach. Sodium bicarbonate was not effective in protecting the maltase and did not exert a favorable influence on its activity.

During the course of these investigations, a fourth patient with chronic diarrhea came to the authors' attention. This child, an infant first seen at the age of 3 months, had suffered for most of this time from a stubborn diarrhea with failure to thrive. Enzyme studies revealed lactase deficiency similar to that described by Holzel[2] in 1959. No sugar could be detected in the urine. The diarrhea could be controlled only when lactose was eliminated from the diet. The child showed also a flat lactose tolerance curve. On a strictly regulated diet this infant improved and started growing normally.

In a well-presented discussion and summary, the authors emphasize the diagnostic criteria for diarrhea conditions caused by carbohydrate intolerance, clues especially valuable being the lactic acid content and the low pH of the feces. The possibility that these conditions involving carbohydrate intolerance may be familial is suggested, but not strongly emphasized. However, Holzel and his co-workers[2] encountered a family in which a younger child suffered more severely from lactase deficiency and a sibling, 10 years of age, suffered from the same deficiency to a milder degree. One of the patients described by Weijers and his associates[1] was the youngest of 4 children; the eldest child, 13 years of age, suffered from a mild form of diarrhea, and the same enzyme deficiency could be demonstrated in both children.

The authors conclude that "deficiencies of carbohydrate splitting enzymes in the intestine may give rise to chronic diarrhea with all the consequences involved, even with arrest of growth,"[1] and that such a diagnosis should be kept in mind as a "cause of intractable diarrhea." These studies are being continued with respect to both the search for satisfactory treatment and the possible hereditary nature of the enzyme deficiency.

RUSSELL J. BLATTNER, M.D.

REFERENCES

1. Weijers, H. A., van de Kamer, J. H., Dicke, W. K., and Ijsseling, J.: Diarrhoea Caused by Deficiency of Sugar Splitting Enzymes. I, Acta paediat. **50:** 55, 1961.
2. Holzel, A., Schwarz, V., and Sutcliffe, K. W.: Defective Lactose Absorption Causing Malnutrition in Infancy, Lancet **I:** 1126, 1959.

Books

The Pathology of Cerebral Palsy.

Abraham Towbin, Springfield, Ill., 1960, Charles C Thomas, Publisher, 208 pages. Price $8.00.

According to the flyleaf, the author presents "a correlated transectional view of the basic pathology of cerebral palsy" to the end that "no longer need the complex variety of etiologic mechanisms involved in cerebral palsy offer formidable problems to clinicians and pathologist. . . . The pathologic mechanisms have now been classified and brought into practical working relationship."

This is certainly what one would hope for in approaching a book with this title but, after reading it, one is not at all sure that "the formidable problems" have all disappeared.

The first portion of the book deals with the definition of cerebral palsy, its general characteristics, its clinical manifestations, and a welcome usable pathologic classification. All of this material is dealt with simply and in concise fashion.

In succeeding chapters the author expands upon each of the divisions included in his pathologic classification: initially, the systemic disturbances which can result in cerebral palsy are described, then the local intracranial processes, and last the developmental defects. The book is well organized, and the illustrations and short illustrative case reviews are clear and helpful.

The most important shortcoming of the text is its brevity; it turns out to be a well-upholstered classification. A more detailed discussion of each of the separate entities would have been so much better. For example, such subjects as cytomegalic inclusion disease and neuronal storage diseases are dealt with all too briefly, so that, as a reference work, the value of this book is much diminished.

In general, the format is pleasing and the outline with which each chapter is begun makes concepts much easier to grasp and interrelate.

There are isolated statements which are open to question, for example, that cytomegalic inclusion disease is found in one third of all newborn infants (p. 111), and that hydranencephaly is due to anoxia.

The last section of the book deals with what the author calls the "oligophrenic triad"—the organic interrelationship of mental deficiency, epilepsy, and cerebral palsy. The concept is well presented.

MARIE VALDES-DAPENA, M.D.

Resuscitation of the Newborn Infant.

Harold Abramson, M.D., St. Louis, 1960, The C. V. Mosby Company, 274 pages, Price $10.00.

This volume is an outgrowth of the Report on Resuscitation of the Newborn Infant by the Special Committee on Infant Mortality of the Medical Society of the County of New York. It represents the endeavors of 24 collaborators in the clinical and laboratory fields.

The subject matter is generally well covered, and especially so in the chapter on physiology and biochemistry. The methods employed to resuscitate newborn infants are clearly described and well illustrated; the mechanical devices used or recommended are listed in tabular form. "At the present time," the author says, "no mechanical resuscitator conforms to ideal specifications, as presently conceived. The chapter on drugs is also excellent; the indiscriminate routine administration of any drug is considered dangerous. Oxygen is held to be the most important agent which can be used in the delivery room. There are extensive references at the end of each chapter which will be of aid to the person interested in a more exhaustive survey.

This book is highly recommended to those who are concerned with the care of newborn infants in the delivery room.

NORMAN KENDALL, M.D.

News and notes*

The American Board of Pediatrics, Inc. certified the following diplomates at Houston, Texas, on March 3 to 5, 1961:

Aballi, Arturo J., Division of Pediatrics, Frank T. Tobey Memorial Children's Hospital, 860 Madison Avenue, Memphis 3, Tennessee
Arky, Albert Milton, St. Albans Naval Hospital, St. Albans, Long Island, New York
Avery, Willard B., 329 Main Street, Boonville, Missouri
Barnes, Martin Wesley, 10269 East Telephone Road, Ventura, California
Bates, Richard Dayton, 109 South Delaware, Irving, Texas
Berg, Bruce O., United States Army Hospital, APO 696, New York, New York
Betts, William Archibald, Jr., 3102 South Harvard, Tulsa, Oklahoma
Bownes, Eugene A., 18520 Grand River, Detroit 23, Michigan
Brennan, Robert Stewart, 2612 Longwood Drive, Foulk Woods, Wilmington 3, Delaware
Carey, Donald Edward, Rockefeller Foundation Virus Research Centre, Poona, India
Clayton, George Wesley, 1200 M. D. Anderson, Houston, Texas
Cornwell, Samuel Owen, 503 Central Avenue, Butner, North Carolina
Crozier, Wallace Allen, Scott and White Clinic, 213 West Avenue G, Temple, Texas
Cummings, Leroy J., Quarters 6451-D, United States Air Force Academy, Colorado
Curtis, Edward George, 1825 West Stadium Boulevard, Ann Arbor, Michigan
Curtis, John C., USAH, Fort Sill, Oklahoma
Dillard, Ruth A., Department of Pediatrics, University of North Carolina, School of Medicine, Chapel Hill, North Carolina
Diserens, Harold William, 234 West Beauregard Avenue, San Angelo, Texas
Dodson, Dwain Freeman, 1430 West Avenue J., San Angelo, Texas
Durham, Henry Stigler, Jr., 112 Coliseum Boulevard, Montgomery 9, Alabama
Ellington, Preston David, 1727 Central Avenue, Augusta, Georgia
Feldman, Robert B., 11891 Plank Road, Baton Rouge, Louisiana
Gagliano, Nicholas C., 1542 Tulane Avenue, New Orleans 12, Louisiana
Garrison, Rufus James, 420 North University Street, Murfreesboro, Tennessee
Glow, Donald Thomas, 304 South 42nd Street, Omaha 31, Nebraska
Goldman, Harold Earl, 3549 South Winston, Tulsa, Oklahoma
Green, Alfred J., 1727 Central Avenue, Augusta, Georgia
Gregory, Robert Edward, 3425 Glenmore Avenue, Cincinnati 11, Ohio
Griffin, John Bunyan, Jr., 323 Nellis Drive, James Connally Air Force Base, Waco, Texas
Harris, Leonard Crossley, Pediatric Department, John Sealy Hospital, Galveston, Texas
Heffner, Ralph Wesley, 3025 West Broward Boulevard, Fort Lauderdale, Florida
Hill, Frank Douglass, III, 1659 Milford, Houston, Texas
Holmes, T. H., Jr., Suite 104, 3610 34th Street, Lubbock, Texas
Jenkins, Cecil Gwinn, 500-K University Plaza, Jackson 6, Mississippi
Jordan, Jerry Dugger, 3325 Westridge Street, Houston, Texas
Kappes, William Carl, Jr., 2440 6th Street, Lake Charles, Louisiana
Kartus, Sam, 1819 29th Avenue South, Birmingham 9, Alabama
Kent, James Roy, 8-B Boatner Drive, Elgin Air Force Base, Florida
Kitchen, Robert N., 401st TAC Hospital, England Air Force Base, Louisiana
Kline, Allen H., 517 Flintdale, Houston 24, Texas
Lipsey, John Crawford, 1710th Air Force Hos-

*Notices of meetings must be in the hands of the Editor 3 months in advance of the date in order to appear in the JOURNAL in time.

pital, Donaldson Air Force Base, Greenville, S. C.

Lowe, Betty Ann, 401 East 5th Street, Texarkana, Arkansas

Lucas, Russell V., Jr., Department of Pediatrics, University of Minnesota Medical School, Minneapolis 14, Minnesota

Massengale, Oliver N., 4200 East 9th Avenue, Denver 20, Colorado

Moroney, John D., 2505 Middleton Avenue, Winter Park, Florida

Morris, Dorothy L., 3800-4100 East Colfax Avenue, Denver 6, Colorado

Most, Bertha Marie, Masonic Hall Building, East State Street, Oakdale, Pennsylvania

Nowack, Jacques, 60 West Winnie Way, Arcadia, California

Parman, Robert D., 306 Medical Arts Building, Topeka, Kansas

Pequet, A. Russell, 334 Canterbury Drive, Corpus Christi, Texas

Petry, Eugene L., University of Kansas Medical Center, 39th at Rainbow, Kansas City, Kansas

Plaut, Samuel Max, 1236 Waterman, San Bernardino, California

Porter, Philip J., 3820 Weyburn Drive, Fort Worth, Texas

Potter, Thomas Edward, 3000 East 78th Street, Chicago 49, Illinois

Rainwater, Weldon T., 527 North 6th Street, Blytheville, Arkansas

Roark, Kenneth LaRue, 1311 Woodland, Johnson City, Tennessee

Ryan, James Herbert, 1309 East Court Street, Kankakee, Illinois

Sasano, Joseph Richard, Jr., Section of Pediatrics, Mayo Clinic, Rochester, Minnesota

Schaffer, James J., Riley Hospital, 3208 North Brouse Street, Indianapolis, Indiana

Schlegel, Robert John, Tripler USAH (USAR PAC) APO 438, San Francisco, Calif.

Scott, Thomas Purcell, Jr., 3305 West Manor Lane, S.W., Atlanta 11, Georgia

Sederstrom, Leslie W., Staff, United States Naval Hospital, Camp Pendleton, California

Spiro, Alfred Jules, United States Public Health Service Hospital, Staten Island 4, New York

Spitz, Richard H., 625 Cleveland Avenue, Columbus 16, Ohio

Sterne, Thomas L., 2701 North Azalea, Victoria, Texas

Tollett, Joe R., 701 South Main, Jacksonville, Texas

Tottori, Mitsuo, Department of Pediatrics, Tulane University Medical School, New Orleans, Louisiana

Travis, Luther Brisendine, 2314 Downey, La Marque, Texas

Van Leeuwen, Gerard J., 410 North Washington, Odessa, Texas

Walker, Colin H. M., University of Colorado Medical Center, 4200 East 9th Avenue, Denver 20, Colorado

Ward, Mary Johnson, 1824 Robison Hill Rd., Montgomery 6, Alabama

Watt, Philip Hon Fai, 1481 South King Street, Honolulu 14, Hawaii

Willis, Kathryn W., 2306 Welborn, Dallas 19, Texas

Wolf, Richard Stanley, 3-160 McNair, Killeen, Texas

Womack, Grover Kenneth, 1402 Nueces, Austin 1, Texas

Wunderlich, Ray Charles, Jr., 2128 Monroe Avenue, Rochester 18, New York

Young, William Frederick, 602 Dove Street, Sumter, South Carolina

Special Foreign Certificates:

Bajoghli, Mehdi, Khajo, Isfahan, Iran

Evangelista, Lavinia Sahagun, A. Flores, City of San Pablo, Philippines

Golding, Robert Lavrence, 36 Exchequer Street, Dublin, Ireland

Hastreiter, Alois Rudolf, Children's Memorial Hospital, 707 Fullerton Avenue, Chicago 14, Illinois

Kim, Chong-Jin, 1610 East 21st Avenue, Denver 5, Colorado

Martinez, Heliodoro Cordoba, Manuel Rivas No. 4, San Luis Potosi, S.L.P., Mexico

Moezi, Khalil, Shahreza Street, Avenue Anvar-Khorwash 160, Tehran, Iran

Noha, Elfi Maria, c/o Josef Noha, München-Obermenzing, Feichthofstr. 92, West Germany

Noorani (Bagherzadeh), Parvin, c/o M. Noorani, M.D., Morrisania City Hospital, New York Bronx 52, New York

Özand, Pinar Tevfik, 4577 McKinley Avenue, St. Louis 10, Missouri

Perez, Remedios B., Asingan, Pangasinan, Philippines

Reddy, D. Venudhar, c/o D. Narsimha Reddy, Naya Nagar, Suriyapet, A.P. India

Sila, Ulgan Inan, 8660 Old Bonhomme, University City 32, Missouri

Ty, Anita N., A. Flores Street, San Pablo City, Philippines

EDITOR'S COLUMN

The enuresis problem in children

THERE is need to review some of the long-held concepts concerning nocturnal enuresis in children and the therapeutic regimens recommended for it. Two publications provide such an opportunity: the one by Bakwin[1] in this issue and a recent one by Muellner.[2]

Bakwin's article provides an excellent summary of the literature with some interpretive comments. In view of his broad experience in the behavioral field, one could have hoped for more in the way of his personal evaluation of some of the controversial concepts. His article, however, is not strictly a review or an interpretive article, since he has added a concept of his own as to the etiology of enuresis in children. He regards enuresis as an inborn developmental disorder characterized by a delay in gaining control of urinary function. In a sense such delay is comparable to that in other functions such as teething, walking, and communication. Moreover, he believes that in the large majority of enuretic children the disorder is self-limited, being outgrown by the age of 6 to 8 years in many, and by the early teens in most, and that, except for symptoms of urgency which persist in a few, all lead normal lives.

In 25 families of medical colleagues containing a child with enuresis, he found a history of bed-wetting in one or both parents in 72 per cent. Although we have no personally recorded data, our experience and that of our colleagues is similar. Such observations suggest that the enuretic child has merely inherited the same faulty mechanism for urinary control possessed by his parents and/or close relatives. As Bakwin states, it is surprising how often parents who were themselves enuretic during childhood fail to understand their child's problem. An appreciation of the familial pattern is frequently effective in letting the child off the hook so far as culpability for willfulness or indifference toward his bed-wetting is concerned. Furthermore, it is usually influential in persuading parents to cease such useless interference as shaming, scolding, punishments, rewards, threats, and coercion.

Developmental delay is applicable to those children who, once the enuresis ceases, are thereafter symptomless. When urinary symptoms—e.g., urgency nocturia, enuresis—continue into adult life, the term "delay" does not seem appropriate. For this group Bakwin suggests that a developmental abnormality probably is present.

This simple etiological concept seems reasonable and fits the majority of the enuretic children in my practice over many years. But, if it is accepted, how does one relate the widely held psychiatric view that enuresis is usually an emotional disturbance, often secondary to a disturbed parent-child relationship? After citing the divergent views, Bakwin concludes that no well-defined abnormal behavioral patterns are characteristic of children with enuresis, and suggests that the minor changes reported in some studies might be explained by the effect of the symptom on the child's behavior. Nor does he agree with those who maintain that enuresis represents "immature" behavior.

He states he has not observed it. Unquestionably there are emotionally disturbed children who have enuresis, but such children usually manifest other abnormal behavior patterns which serve to identify them as being emotionally disturbed. Their histories differ from those of children who have enuresis as the sole complaint. The emotionally disturbed child who happens to have enuresis as one manifestation of a mental illness should be sharply differentiated from the otherwise normal and emotionally stable child who wets the bed because of a temporarily faulty urinary mechanism inherited from his parents.

Similarly the view that enuresis may be due to an abnormality of the urogenital tract merits consideration. Here again Bakwin reviews a number of studies and concludes that "anatomical changes in the urogenital tract are rare causes of enuresis in children." However, he stresses the need to examine the urine to exclude the possibility of diabetes mellitus, diabetes insipidus, or infection of the urinary tract. Symptoms such as a small urinary stream, difficulty in starting the stream, or dribbling suggest the possibility of a congenital defect along the genitourinary tract and are indications for a careful urologic investigation.

Nor are the usual definitions of enuresis to be accepted at face value. For instance, it is commonly stated that the child who has not acquired nocturnal urinary control by 3 years of age should be classed as enuretic. Considering the rather complicated developmental mechanism necessary to achieve voluntary control as described by Muellner,[2] 3 years of age seems too early to stigmatize the child as an enuretic. Five years of age would appear to be a better dividing line, and it would provide the basis for parental reassurance for two more years.

There is also the issue of the relation of depth of sleep to bed-wetting. If the potentially enuretic child's sleep is so deep that the need to empty his bladder does not rouse him to consciousness and he wets the bed, he is considered enuretic. On the other hand, if his sleep is not quite so deep and he responds to the urge to urinate by emptying his bladder in the toilet, he is not considered to be enuretic but is commended for his ability to care for himself. In a sense, then, in this group of potentially enuretic children, depth of sleep may be the determining factor in regard to bed-wetting. One may ask, "Does depth of sleep differ in enuretic and nonenuretic children?" and "Is depth of sleep also an inherited quality?" Quantitative, properly controlled studies are not available, but Bakwin cites several studies which suggest that deep sleepers are more frequent among enuretic than among the nonenuretic individuals. The observations of several authors cited by Bakwin that the incidence of abnormal electroencephalograms and, to a lesser extent, of convulsions is significantly greater among enuretic children than among the nonenuretic are somewhat disturbing. Although we find it difficult to believe that there is a correlation, the possibility of a relationship should be investigated further. We have not routinely obtained electroencephalograms on our enuretic children, but we are not aware of an increased frequency of epilepsy among them or their families.

Muellner[2] also proposes a definite etiological concept of enuresis and suggests a plan of therapy based on it. By fluoroscopic observations of more than 1,000 children, Muellner has demonstrated the developmental steps from the infantile to the adult type of bladder control. He concludes that bladder control is a self-learned skill which normally occurs between the ages of 2 and 4½ years. During the transformation from infantile automatic bladder control to the coordinated use of the levator ani, the thoracic diaphragm, and the abdominal musculature which contribute to the voluntary mechanism of bladder control, the infant's bladder doubles in capacity from the age of 2 to 4½ years. In primary enuresis, he describes a failure of normal maturational development resulting in a bladder too small for the child's age. The treatment recommended by Muellner is the forcing of fluids during the day with instruction of the child

to hold his urine as long as possible in order to enlarge and distend the bladder. Duration of treatment is from 3 to 6 months. In the meantime Muellner advises that the commonly employed therapeutic measures, which he considers to be ineffective, be abandoned; these include "dehydration, the strict forbidding of fluid after 4:00 P.M., dragging the child out of his bed at night to void, clocks to wake him, and gadgets to shock him out of his sleep once involuntary leakage of urine has occurred. Equally futile are rewards and punishments for something a child cannot control without help."

It would appear that the etiological concepts of nocturnal enuresis advanced by Bakwin and Muellner can be combined. Thus, enuresis could be considered to be on a hereditary basis with a developmental delay in the acquisition of bladder control as stated by Bakwin with an explanation for the developmental delay provided by the studies of Muellner. The two workers differ mainly in the therapeutic measures recommended.

LEE FORREST HILL, M.D.

REFERENCES

1. Bakwin, Harry: Enuresis in Children, J. Pediat. **58:** 806, 1961.
2. Muellner, S. Richard: Development of Urinary Control in Children; Some of the Causes and Treatment of Primary Enuresis, J. A. M. A. **172:** 1256, 1960.

Revision of the National Board of Medical Examiners tests completed

THE announcement by the National Board of Medical Examiners that an improved Part III examination has been developed and will be put into use in June of this year is of interest, as many pediatricians take part in the administration of this 2-day test.

In the late forties the Board, after considerable discussion and investigation, and despite some objection, decided to change the written examinations in Part I and Part II from the "essay" type, which had been used for 25 years, to the "multiple-choice" type of examination. A partial trial in 2 subjects in 1951 was so encouraging that 5 full-length tests were given in 1952 (pediatrics was one), and in 1953 a complete changeover was made. For each of the 12 subjects now included in the examinations there is an examination committee of 6 or 7 for the particular subject with staggered terms of 4 years. Thus around 75 teachers from medical schools in all parts of the country take an active part in the preparation of the tests. Each committee meets for 2 days once a year to prepare the questions, but the grading, which was a formidable and unsatisfactory task with the "essay" type, is done accurately by mechanical means in the Board office in Philadelphia. The first pediatric committee consisted of Drs. Barnett, Schwenkter, Senn, Veeder, and Weech. The present committee consists of Drs. Aldrich, Cooke, Krugman, McCrory, Miller, and Vaughan.

With Parts I and II changed and running smoothly, the Board turned its attention to Part III, the oral examination given after a year of internship to test the candidate's ability to *apply* the knowledge tested in Parts I and II. This part is given each June in some 40 centers by "subsidiary boards," with several of them in some metropolitan centers with a large number of candidates. The problems were quite different from those faced in Parts I and II, and the Board appreciated that there was much to be learned about testing the skills that define clinical competency at the intern level. A

grant was therefore obtained from the Rockefeller Foundation for a study of the problem. After 2 years, with the cooperation of the American Institute for Research, entirely new procedures for conducting the Part III test have been evolved. A trial test was made in 2 centers in January, preparatory to its nationwide administration in June of this year. Details are being issued by the Board.

While on the subject of the Board there is a story which is probably unknown to most pediatricians. Although the Board was founded in 1915, not until 20 years later was a pediatrician included in its membership. To bring this about took considerable "pressure" in the thirties. Dr. A. Graeme Mitchell was the first appointee, and after his untimely death in 1941 he was succeeded by Dr. Veeder. It was not until a few years later, however, that the Board recognized pediatrics as one of the major fields of clinical medicine and made the subject a separate examination in Part II and included it in Part III. In the late forties the position of Executive Secretary to the Board became open and Dr. Veeder, who was president at the time, recommended the appointment of Dr. John P. Hubbard, who had recently directed the Survey of Child Health for the Academy of Pediatrics. Dr. Hubbard has been responsible for carrying out all of the studies and the details involved in the revamping of the Board's tests. Today, practically every State Board of Licensure recognizes the National Board certificate, and last year 75 per cent of the class members in 55 of our medical schools took National Board examinations. Thus pediatrics—an unwanted child only a few years ago—has had an active part in the changes that have taken place in the character of the Board's examinations and the scope of their usefulness.

Index to Volume 58

*Author index**

A

ALBAN, JAN. Griscofulvin therapy in tinea capitis, 367

AMBUEL, J. PHILIP. An evaluation of resident training in the outpatient department, 272

ARCASOY, MUFIT. (*See* RASHKIND, GOLINKO, AND ARCASOY), 464

ARCILLA, RENE A., AND GASUL, BENJAMIN M. Congenital aplasia or marked hypoplasia of the myocardium of the right ventricle (Uhl's anomaly), 381

— and —. Congenital dextrocardia, 39

— and —. Congenital dextrocardia (conclusion), 251

B

BAKWIN, HARRY. Enuresis in children, 806

BARNETT, HENRY L. (*See* KORSCH AND BARNETT), 707

BARRIE, HERBERT. (*See* BUCCI, COOK, AND BARRIE), 820

BAYLIN, GEORGE J. (*See* CASTLE AND BAYLIN), 404

BERNSTEIN, JAY. (*See* RUBENSTEIN, MEYER, AND BERNSTEIN), 356

BIGELOW, EUGENE L. Changing concepts concerning mastocytosis, 499

BLATTNER, RUSSELL J. Antihemophilic globulin levels in carriers of hemophilia A, 298

—. Complications of viral hepatitis, 596

—. Diarrhea caused by deficiency of sugar-splitting enzymes, 883

—. Photic seizures—television-induced, 746

—. Rabies infection transmitted by insectivorous bats: human case with virus isolation from spinal fluid during life, 433

—. Recent findings concerning viremia in the human subject, 134

BONGIOVANNI, ALFRED M. (*See* LEBOEUF, BONGIOVANNI, STEIKER, AND EBERLEIN), 477

—. (*See* STEIKER, MELLMAN, BONGIOVANNI, EBERLEIN, AND LEBOEUF), 321

BRAZELTON, T. BERRY. Psychophysiologic reactions in the neonate. I. The value of observation of the neonate, 508

—. Psychophysiologic reactions in the neonate, II. Effect of maternal medication on the neonate and his behavior, 513

BROWDER, ANN A. (*See* FEINSTEIN, PETERSDORF, AND BROWDER), 164

—. (*See* PETERSDORF, BROWDER, AND FEINSTEIN), 174

BROWN, JOHN H. (*See* MIDDELKAMP, HERWEG, THORNTON, BROWN, AND REED), 205

BROWN, WEBSTER H. Anterior fontanel bone, 800

BUCCI, GIOVANNI, COOK, CHARLES D., AND BARRIE, HERBERT. With the technical assistance of Joanna F. Hamann. Studies of respiratory physiology in children. V. Total lung diffusion, diffusing capacity of pulmonary membrane and pulmonary capillary blood volume in normal subjects from 7 to 40 years of age, 820

BUTLER, HARRY G. (*See* FRENCH, CLARK, BUTLER, AND TEASDALL), 17

BYERS, RANDOLPH K. Bronson Crothers (1884-1959), 438

C

CALCAGNO, PHILIP L., AND RUBIN, MITCHELL I. Physiologic considerations concerning corticosteroid therapy and complications in the nephrotic syndrome (Symposium), 686

CASTLE, ROBERT F., AND BAYLIN, GEORGE J. Severe acquired mitral stenosis in childhood and adolescence, 404

CHAO, DORA HSI-CHIH, AND PLUMB, RICHARD L. Diamox in epilepsy, 211

CHEEK, DONALD B. Extracellular volume: its structure and measurement and the influence of age and disease, 103

CHIONG, ROSITA. (*See* SHOSHKES, WILLNER, PONTORIERO, AND CHIONG), 27

CLARK, DAVID B. (*See* FRENCH, CLARK, BUTLER, AND TEASDALL), 17

COBURN, ALVIN F. Susceptibility to rheumatic disease (editorial), 448

COLLADO, MANUEL. (*See* DONNELL, COLLADO, AND KOCH), 836

COLLINS, W. F., AND PUCCI, G. L. Peritoneal drainage of subdural hematomas in infants, 482

COMSTOCK, GEORGE W. (*See* DAVIS AND COMSTOCK), 771

COOK, CHARLES D. (*See* BUCCI, COOK, AND BARRIE), 820

CRAMBLETT, HENRY G., AND FOMON, SAMUEL J. Unpredictability of antibody response of infants to injections of Salk poliomyelitis vaccine, 779

*January, pp. 1-148; February, pp. 149-304; March, pp. 305-454; April, pp. 455-606; May, pp. 607-760; June, pp. 761-908.

CUMMING, G. R., AND FINKEL, K. Intracardiac myxoma involving the right and left atria in a young patient, 559
CUMMINS, LEO H. Hypoglycemia and convulsions in children following alcohol ingestion, 23

D

DAVIS, STARKEY D., AND COMSTOCK, GEORGE W. Mycobacterial cervical adenitis in children, 771
DEDIANOUS, NOEL. (*See* WOODY, DEDIANOUS, AND WOODY), 738
DISBROW, MILDRED A. (*See* PARMELEE, SCHULZ, AND DISBROW), 241
DOBBINS, WILLIAM T. (*See* ETTELDORF, DOBBINS, SUMMITT, RAINWATER, AND FISCHER), 226
DONNELL, GEORGE N., COLLADO, MANUEL, AND KOCH, RICHARD. Growth and development of children with galactosemia, 836

E

EBERLEIN, WALTER R. (*See* LEBOEUF, BONGIOVANNI, STEIKER, AND EBERLEIN), 477
—. (*See* STEIKER, MELLMAN, BONGIOVANNI, EBERLEIN, AND LEBOEUF), 321
EDELMANN, CHESTER M., JR. (*See* SAND AND EDELMANN), 845
EMANUEL, B., AND SCHOENFELD, A. Favism in a nursing infant, 263
ENGLE, MARY ALLEN. (*See* MASTER, ENGLE, STERN, AND SMITH), 455
ETTELDORF, JAMES N., DOBBINS, WILLIAM T., SUMMITT, ROBERT L., RAINWATER, WELDON T., AND FISCHER, ROBERT L. Intermittent peritoneal dialysis using 5 per cent albumin in the treatment of salicylate intoxication in children, 226
—. (*See* SMITH AND ETTELDORF), 1

F

FELDMAN, G. V. (*See* GAISFORD, FELDMAN, AND PERKINS), 493
FEINSTEIN, ALVAN R., PETERSDORF, ROBERT G., AND BROWDER, ANN A. Prophylaxis of poststreptococcal sequelae and bacterial endocarditis, 164
—. (*See* PETERSDORF, BROWDER, AND FEINSTEIN), 174
FIELDS, JOHN P. Bulging fontanel: a complication of tetracycline therapy in infants, 74
FINKEL, K. (*See* CUMMING AND FINKEL), 559
FISCHER, ROBERT L. (*See* ETTELDORF, DOBBINS, SUMMITT, RAINWATER, AND FISCHER), 226
FLEISHER, DANIEL S. Cation exchange resin therapy for hyperkalemia in infants and children, 486
FLORMAN, ALFRED L. Some newly described viruses and diseases associated with them, 286
FOLL, C. V. Hospital admissions for pediatric accidents in Upper Assam, 93
FOMON, SAMUEL J. (*See* CRAMBLETT AND FOMON), 779
FRAIN-BELL, WILLIAM, AND KOBLENZER, PETER J. Toxic epidermal necrolysis, 722
FREEDMAN, DANIEL X. (*See* SCHAIN AND FREEDMAN), 315
FRENCH, JOSEPH H., CLARK, DAVID B., BUTLER, HARRY G., AND TEASDALL, ROBERT D. Phenylketonuria: some observations on reflex activity, 17
—. (*See* GILLES AND FRENCH), 195

G

GAISFORD, WILFRID, FELDMAN, G. V., AND PERKINS, F. T. The response of infants to poliomyelitis immunization after neonatal immunization with triple antigen, 493
GASUL, BENJAMIN M. (*See* ARCILLA AND GASUL), 39
—. (*See* ARCILLA AND GASUL), 251
—. (*See* ARCILLA AND GASUL), 381
GILLES, FLOYD H., AND FRENCH, JOSEPH H. Postinjection sciatic nerve palsies in infants and children, 195
GILLIS, C. N. (*See* TAYLOR, GILLIS, NASH, AND KULLMAN), 470
GLENN, MORTON B. An adult problem—a pediatric challenge, 304
GOLINKO, RICHARD. (*See* RASHKIND, GOLINKO, AND ARCASOY), 464
GOLUBOFF, NATHAN, AND WHEATON, ROSS. Methylene blue induced cyanosis and acute hemolytic anemia complicating the treatment of methemoglobinemia, 86
GOTLIEB, A., PESACH, J., AND RIMON, A. The role of lysolecithin and cholesterol in icterus neonatorum, 829
GOOD, ROBERT A. (*See* VERNIER, WORTHEN, AND GOOD), 620
GRONDAHL, RAYMOND D. (*See* HILL, PETERSON, GRONDAHL, AND KRIPPAEHNE), 59

H

HAGGARD, MARY ELLEN, AND SCHNEIDER, ROSE G. Sickle cell anemia in the first 2 years of life, 785
HAMANN, JOANNA. (*See* BUCCI, COOK, AND BARRIE), 820
HANSHAW, JAMES B., AND WELLER, THOMAS H. Urinary excretion of cytomegaloviruses by children with generalized neoplastic disease, 305
HARRIS, LLOYD E. (*See* HEMPLE, HARRIS, SVIEN, AND HOLMAN), 342
HARTMANN, ALEXIS F., SR., WOHLTMANN, HULDA J., AND HOLOWACH, JEAN. Recognition and investigation of hypoglycemia, 864
HEMPLE, DEAN J., HARRIS, LLOYD E., SVIEN, HENDRIK J., AND HOLMAN, COLIN B. Craniosynostosis involving the sagittal suture only: Guilt by association? 342
HERWEG, JOHN C. (*See* MIDDELKAMP, HERWEG, THORNTON, BROWN, AND REED), 205
HEYMANN, WALTER. Pathogenesis of the nephrotic syndrome: considerations based on clinical and experimental studies (Symposium), 609

HILL, ALLAN J., JR., PETERSON, CLARE G., GRONDAHL, RAYMOND D., AND KRIPPAEHNE, WILLIAM W. Conjoined thoracopagus twins, 59
HILL, LEE FORREST. The enuresis problem in children (editorial), 889
HOLMAN, COLIN B. (*See* HEMPLE, HARRIS, SVIEN, AND HOLMAN), 342
HOLOWACH, JEAN. (*See* HARTMANN, WOHLTMANN, AND HOLOWACH), 864
HOLT, L. EMMETT, JR. (*See* SNYDERMAN AND HOLT), 237
HUANG, NANCY. (*See* KLEIN AND HUANG), 312

I

ILLINGWORTH, R. S. Delayed maturation in development, 761

J

JAMES, DAVID H., JR. Spontaneous rupture of the stomach, 849
JANEWAY, CHARLES A. (*See* METCOFF AND JANEWAY), 640
JOE, LIE KIAN (*See* SUPRIHATIN AND JOE), 100
JORESS, SUMNER M. (*See* SOLOMON, WEINSTEIN, AND JORESS), 716
JOY, ROBERT C. (*See* STAHL AND JOY), 373

K

KAHN, E. Pediatrics in an industrialized part of Africa, 277
KLEIN, MORTON, AND HUANG, NANCY. The response of infants and children to Asian influenza vaccine administered by intradermal and subcutaneous routes, 312
KLEIN, R. (*See* MARKS, WOLFSON, AND KLEIN), 32
KOBLENZER, PETER J. (*See* FRAIN-BELL AND KOBLENZER), 722
KOCH, RICHARD. (*See* DONNELL, COLLADO, AND KOCH), 836
KORSCH, BARBARA, AND BARNETT, HENRY L. The physician, the family, and the child with nephrosis (Symposium), 707
KRIPPAEHNE, WILLIAM W. (*See* HILL, PETERSON, GRONDAHL, AND KRIPPAEHNE), 59
KULLMAN, G. L. (*See* TAYLOR, GILLIS, NASH, AND KULLMAN), 470

L

LANE, MARGARET R. Maple syrup urine disease, 80
LEBOEUF, GILLES, BONGIOVANNI, ALFRED M., STEIKER, DANIEL D., AND EBERLEIN, WALTER R. Immunologic and thyroid function studies in euthyroid children with goiter, 477
—. (*See* STEIKER, MELLMAN, BONGIOVANNI, EBERLEIN, AND LEBOEUF), 321
LINCOLN, EDITH M. (*See* ZITRIN AND LINCOLN), 219
DE LISSOVOY, VLADIMIR. Head banging in early childhood, 803

M

MCCUE, CAROLYN M., AND YOUNG, R. B. Cardiac failure in infancy, 330
MCLELLAN, M. S., AND WEBB, CLARENCE H. Ear studies in the newborn infant. II. Age of spontaneous visibility of the auditory canal and tympanic membrane, and the appearances of these structures in healthy newborn infants, 523
MARKS, J., WOLFSON, J., AND KLEIN, R. Neonatal thyroid function: erythrocyte T_3 uptake in early infancy, 32
MASTER, JER, ENGLE, MARY ALLEN, STERN, GERTRUDE, AND SMITH, CARL H.: Cardiac complications of chronic, severe refractory anemia with hemochromatosis. I. Acute pericarditis of unknown etiology, 455
MATSON, DONALD D. (*See* SCHICK AND MATSON), 791
MELLMAN, WILLIAM J. (*See* STEIKER, MELLMAN, BONGIOVANNI, EBERLEIN, AND LEBOEUF), 321
METCOFF, JACK. Symposium on nephrotic syndrome: introduction, 607
—, AND JANEWAY, CHARLES A. Studies on the pathogenesis of nephrotic edema (Symposium), 640
MEYER, RUBEN. (*See* RUBENSTEIN, MEYER, AND BERNSTEIN), 356
MIDDELKAMP, J. NEAL, HERWEG, JOHN C., THORNTON, HELEN K., BROWN, JOHN H., AND REED, CHARLES A. Viral meningoencephalitis, 205
MONCRIEFF, ALAN. Sir Robert Hutchison, Bart. (1871-1960), 137
MOODIE, AILEEN. Kwashiorkor in Cape Town: the background of patients and their progress after discharge, 392
MORTIMER, EDNA Z. Anaphylaxis following ingestion of soybean, 90

N

NASH, C. W. (*See* TAYLOR, GILLIS, NASH, AND KULLMAN), 470
NELSON, WALDO E. A pediatric career (editorial), 147
—. Revision of the National Board of Medical Examiners tests completed (editorial), 891
NETER, ERWIN. (*See* ROSENTHAL, NETER, AND WEPPNER), 377

P

PARMELEE, ARTHUR HAWLEY, SR. Thoughts about pediatrics (editorial), 451
PARMELEE, ARTHUR H., JR., SCHULZ, HELEN R., AND DISBROW, MILDRED A. Sleep patterns of the newborn, 241
PERKINS, F. T. (*See* GAISFORD, FELDMAN, AND PERKINS), 493
PESACH, J. (*See* GOTLIEB, PESACH, AND RIMON), 829

PETERSDORF, ROBERT G. Symposium on the chemoprophylaxis of infection. I. Introduction and general principles, 149
—, BROWDER, ANN A., AND FEINSTEIN, ALVAN R. Protection against infection in susceptible individuals, 174
—, AND WOODWARD, THEODORE E. The use of antibiotics to prevent infections by specific pathogens, 153
—. (*See* FEINSTEIN, PETERSDORF, AND BROWDER), 164
PETERSON, CLARE G. (*See* HILL, PETERSON, GRONDAHL, AND KRIPPAEHNE), 59
PHELPS, JANE. (*See* THELANDER AND PHELPS), 389
PINKEL, DONALD. Chickenpox and leukemia, 729
PLUMB, RICHARD L. (*See* CHAO AND PLUMB), 211
PONTORIERO, GIACOMO. (*See* SHOSHKES, WILLNER, PONTORIERO, AND CHIONG), 27
PUCCI, G. L. (*See* COLLINS AND PUCCI), 477

R

RAINWATER, WELDON T. (*See* ETTELDORF, DOBBINS, SUMMITT, RAINWATER, AND FISCHER), 226
RASHKIND, WILLIAM J., GOLINKO, RICHARD, AND ARCASOY, MUFIT, Cardiac findings in idiopathic hypercalcemia of infancy, 464
REED, CHARLES A. (*See* MIDDELKAMP, HERWEG, THORNTON, BROWN, AND REED), 205
REID, D. H. S. Acute infantile beriberi, 858
RIMON, A. (*See* GOTLIEB, PESACH, AND RIMON), 829
ROSENTHAL, AMNON, NETER, ERWIN, AND WEPPNER, DAVID F. Recovery from Salmonella meningitis after treatment with furaltadone (Altafur), 377
RUBENSTEIN, MARC, MEYER, RUBEN, AND BERNSTEIN, JAY. Congenital abnormalities of the urinary system, 356
RUBIN, MITCHELL I. (*See* CALCAGNO AND RUBIN), 686

S

SAND, RICHARD E., AND EDELMANN, CHESTER M., JR. Pyridium-induced methemoglobinemia, 845
SCHAIN, RICHARD J., AND FREEDMAN, DANIEL X. Studies on 5-hydroxyindole metabolism in autistic and other mentally retarded children, 315
SCHICK, ROBERT W., AND MATSON, DONALD D. What is arrested hydrocephalus? 791
SCHNEIDER, ROSE G. (*See* HAGGARD AND SCHNEIDER), 785
SCHOENFELD, A. (*See* EMANUEL AND SCHOENFELD), 263
SCHULZ, HELEN R. (*See* PARMELEE, SCHULZ, AND DISBROW), 241
SCOTT, EDWIN P., AND STEIGMAN, ALEX J. Accidental isolated primary vaccinia of the tongue, 77
SHOSHKES, MILTON, WILLNER, MILTON, PONTORIERO, GIACOMO, AND CHIONG, ROSITA. "Solubilized" vitamin K_1 (phytonadione) in neonatal hypoprothrombinemia, 27
SHURTLEFF, DAVID B. Meconium peritonitis presenting as an abdominal mass, 267
SILBER, EARL N. (*See* WEIS AND SILBER), 548
SILVERMAN, WILLIAM A. The effect of the atmospheric environment on the premature infant, 581
SMITH, CARL H. (*See* MASTER, ENGLE, STERN, AND SMITH), 455
SMITH, HARRIS L., AND ETTELDORF, JAMES N. Parenteral fluid regimens in the treatment of severe diarrhea in infants, 1
SNYDER, C. HARRISON, AND WHITE, ROY S. Successful treatment of Histoplasma meningitis with amphotericin B, 554
SNYDERMAN, SELMA E., AND HOLT, L. EMMETT, JR. The effect of high caloric feeding on the growth of premature infants, 237
SOLOMON, PAUL, WEINSTEIN, LOUIS, AND JORESS, SUMNER M. Studies of the incidence of carriers of enteropathogenic Escherichia coli in a pediatric population, 716
STAHL, WILLIAM M., JR., AND JOY, ROBERT C. Chylous cysts of the mesentery in infants, 373
STEIGMAN, ALEX J. (*See* SCOTT AND STEIGMAN), 77
STEIKER, DANIEL D., MELLMAN, WILLIAM J., BONGIOVANNI, ALFRED M., EBERLEIN, WALTER R., AND LEBOEUF, GILLES. Turner's syndrome in the male, 321
—. (*See* LEBOEUF, BONGIOVANNI, STEIKER, AND EBERLEIN), 477
STERN, GERTRUDE. (*See* MASTER, ENGLE, STERN, AND SMITH), 455
STORM, ROBERT R. (*See* ZIEGRA AND STORM), 852
STORVICK, CLARA A. (*See* TANK AND STORVICK), 528
SUMMITT, ROBERT L. (*See* ETTELDORF, DOBBINS, SUMMITT, RAINWATER, AND FISCHER), 226
SUPRIHATIN, S. D., AND JOE, LIE KIAN. The problem of sending fecal specimens to a laboratory for the isolation of pathogenic Escherichia coli in tropical countries, 100
SVIEN, HENDRIK H. (*See* HEMPLE, HARRIS, SVIEN, AND HOLMAN), 342

T

TANK, GERTRUDE, AND STORVICK, CLARA A. Dental caries experience of school children in Corvallis, Oregon, after 7 years of fluoridation of water, 528
TAYLOR, W. C., GILLIS, C. N., NASH, C. W., AND KULLMAN, G. L. Experimental observations on cardiac arrhythmia during exchange transfusion in rabbits, 470
TEASDALL, ROBERT D. (*See* FRENCH, CLARK, BUTLER, AND TEASDALL), 17
TENGG, NIC E. (*See* YOW AND TENGG), 538
THELANDER, H. E., AND PHELPS, JANE. Programing for children with a neurological deficit, 389

THORNTON, HELEN K. (*See* MIDDELKAMP, HERWEG, THORNTON, BROWN, AND REED), 205

TOOLAN, JAMES M. The legal rights of the child (editorial), 605

V

VEEDER, BORDEN S. A pediatric ethical question (editorial), 604

—. Psychiatry and the Tower of Babel, 303

VERNIER, ROBERT L., WORTHEN, HOWARD G., AND GOOD, ROBERT A. The pathology of the nephrotic syndrome (Symposium), 620

W

WEBB, CLARENCE H. (*See* MCLELLAN AND WEBB), 523

WEINSTEIN, LOUIS. (*See* SOLOMON, WEINSTEIN, AND JORESS), 716

WEIS, ERNEST I., AND SILBER, EARL N. Acute constrictive pericarditis, 548

WELLER, THOMAS H. (*See* HANSHAW AND WELLER), 305

WEPPNER, DAVID F. (*See* ROSENTHAL, NETER, AND WEPPNER), 377

WEST, CLARK D. The parenteral fluid therapy of diarrhea: regimens reconciled (editorial), 144

WHEATON, ROSS. (*See* GOLUBOFF AND WHEATON), 86

WHITE, ROY S. (*See* SNYDER AND WHITE), 554

WILLNER, MILTON. (*See* SHOSHKES, WILLNER, PONTORIERO, AND CHIONG), 27

WINICK, MYRON. The relationship of growth and differentiation in the developing embryo, 519

WOHLTMANN, HULDA J. (*See* HARTMANN, WOHLTMANN, AND HOLOWACH), 864

WOLFSON, J. (*See* MARKS, WOLFSON, AND KLEIN), 32

WOODWARD, THEODORE E. (*See* PETERSDORF AND WOODWARD), 153

WOODY, HANNAH B. (*See* WOODY, DEDIANOUS, AND WOODY), 738

—. (*See* WOODY AND WOODY), 568

WOODY, NORMAN C., DEDIANOUS, NOEL, AND WOODY, HANNAH B. American trypanosomiasis. II. Current serologic studies in Chagas' disease, 738

—, AND WOODY, HANNAH B. American trypanosomiasis. I. Clinical and epidemiologic background of Chagas' disease in the United States, 568

WORTHEN, HOWARD G. (*See* VERNIER, WORTHEN, AND GOOD), 620

Y

YOUNG, R. B. (*See* MCCUE AND YOUNG), 330

YOW, MARTHA DUKES, AND TENGG, NIC E. The use of kanamycin sulfate as a therapeutic agent for infants and children, 538

Z

ZIEGRA, SUMNER ROOT, AND STORM, ROBERT R. Dosage of chloramphenicol in premature infants, 852

ZITRIN, CHARLOTTE M., AND LINCOLN, EDITH M. Initial tuberculous infection due to drug-resistant organisms, 219

*Subject Index**

A

Abdominal mass, meconium peritonitis presenting as (Shurtleff), 267
Abnormalities, congenital, of urinary system (Rubenstein, Meyer, and Bernstein), 356
Accidents, pediatric, in Upper Assam, hospital admissions for (Foll), 93
Acute hemolytic anemia complicating treatment of methemoglobinemia, methylene blue induced cyanosis and (Goluboff and Wheaton), 86
infantile beriberi (Reid), 858
Adenitis, cervical, mycobacterial, in children (Davis and Comstock), 771
Adenovirus, whooping cough and (CPC), 876
Adolescence, severe acquired mitral stenosis in childhood and (Castle and Baylin), 404
Adult problem—a pediatric challenge? (Glenn), 304
Africa, pediatrics in an industrialized part of (Kahn), 277
Age and disease, extracellular volume: structure and measurement and influence of (Cheek), 103
Alcohol ingestion, hypoglycemia and convulsions in children following (Cummins), 23
Altafur, recovery from Salmonella meningitis after treatment with (Rosenthal, Neter, and Weppner), 377
American trypanosomiasis. I. (Woody and Woody), 568
II. (Woody, DeDianous, and Woody), 738
Amphotericin B, successful treatment of Histoplasma meningitis with (Snyder and White), 554
Anaphylaxis following ingestion of soybean (Mortimer), 90
Anemia, acute hemolytic, complicating treatment of methemoglobinemia, methylene blue induced cyanosis and (Goluboff and Wheaton), 86
chronic, severe, refractory with hemochromatosis, cardiac complications (Master et al.), 455
sickle cell, in first 2 years of life (Haggard and Schneider), 785
Angiocardiographic, clinical, and autopsy studies on 50 patients. Congenital dextrocardia (concluded) (Arcilla and Gasul), 251
Anomaly, Uhl's congenital aplasia or marked hypoplasia of myocardium of right ventricle (Arcilla and Gasul), 381
Anterior fontanel bone (Brown), 800
Antibiotics to prevent infections by specific pathogens. II. (Symposium) (Petersdorf and Woodward), 153
Antibody response of infants to injections of Salk poliomyelitis vaccine, unpredictability of (Cramblett and Fomon), 779
Antigen, triple, response of infants to poliomyelitis immunization after neonatal immunization with (Gaisford, Feldman, and Perkins), 493
Antihemophilic globulin levels in carriers of hemophilia A (Blattner), 298
Aplasia, congenital, or marked hypoplasia of myocardium of right ventricle (Uhl's anomaly) (Arcilla and Gasul), 381
Arrested hydrocephalus, what is (Schick and Matson), 791
Arrhythmia, cardiac, during exchange transfusion in rabbits, experimental observations on (Taylor et al.), 470
Asian influenza vaccine administered by intradermal and subcutaneous routes, response of infants and children to (Klein and Huang), 312
Assam, Upper, hospital admissions for pediatric accidents in (Foll), 93
Atmospheric environment, effect, on premature infants (Silverman), 581
Atria, right and left, intracardiac myxoma involving (Cumming and Finkel), 559
Auditory canal and tympanic membrane, age of spontaneous visibility of (McLellan and Webb), 523
Autistic and mentally retarded children, studies on 5-hydroxyindole metabolism (Schain and Freedman), 315
Autopsy studies on 50 patients, clinical, angiocardiographic and. Congenital dextrocardia (concluded) (Arcilla and Gasul), 251

B

Babel, Tower of, psychiatry and (editorial), 303
Bacterial endocarditis, prophylaxis of poststreptococcal sequelae and. III. (Symposium) (Feinstein, Petersdorf, and Browder), 174
Banging, head, in early childhood (de Lissovoy), 803
Bats, insectivorous, rabies infection transmitted by, human case with virus isolation from spinal fluid during life (Blattner), 433
Beriberi, infantile, acute (Reid), 858

*January, pp. 1-148; February, pp. 149-304; March, pp. 305-454; April, pp. 455-606; May, pp. 607-760; June, pp. 761-908.

Blood volume, pulmonary capillary, diffusing capacity of pulmonary membrane and total lung diffusion (Bucci, Cook, and Barrie), 820
Books:
Blood diseases of infancy and childhood (Smith), 751
Fundamentals and possibilities in anti-tuberculosis vaccination (Prigge and Heymann), 751
Insulin (Young, editor), 600
Intraspinal tumors of childhood (Rand and Rand), 445
Metabolic basis of inherited disease (Stanbury, Wyngaarden, and Fredrickson, editors), 600
Modern problems in pediatrics—VI (Hotlinger and Berger, editors), 445
Pathology of cerebral palsy (Towlin), 886
Projective techniques with children (Rabin and Haworth, editors), 750
Resuscitation of the newborn infant (Abramson), 886
Review of medical microbiology (Jawetz, Melnick, and Adelberg), 750
Studies on the technique of skin testing in allergy (van der Bijl), 445
Thyroid gland (Myant, editor), 601
Bone, anterior fontanel (Brown), 800
Bronson Crothers (1884-1959) (Byers), 438

C

Caloric feeding, high, on growth of premature infants, effect of (Synderman and Holt), 237
Cape Town, kwashiorkor in, background of patients and progress after discharge (Moodie), 392
Capillary blood volume, pulmonary, total lung diffusion, diffusing capacity of pulmonary membrane and (Bucci, Cook, and Barrie), 820
Cardiac arrhythmia during exchange transfusion in rabbits, experimental observations on (Taylor et al.), 470
complications of chronic, severe, refractory anemia with hemochromatosis (Master et al.), 455
failure in infancy (McCue and Young), 330
findings in idiopathic hypercalcemia of infancy (Rashkind, Golinko, and Arcasoy), 464
Career, pediatric (editorial), 147
Caries, dental, experience of school children in Corvallis, Oregon, after 7 years of fluoridation of water (Tank and Storvick), 528
Carriers of enteropathogenic Escherichia coli in pediatric population, incidence of (Soloman, Weinstein, and Joress), 716
of hemophilia A, antihemophilic globulin levels in (Blattner), 298
Cation exchange resin therapy for hyperkalemia in infants and children (Fleisher), 486
Cervical adenitis, mycobacterial, in children (Davis and Comstock), 771
Chagas' disease, current serologic studies. American trypanosomiasis (Woody, deDianous, and Woody), 738
in United States, clinical and epidemiologic background of American trypanosomiasis (Woody and Woody), 568
Chemoprophylaxis of infection. I. Introduction and general principles, symposium on (Petersdorf), 149
Chickenpox and leukemia (Pinkel), 729
Child, legal rights of (editorial), 605
with nephrosis, physician, family, and (Symposium) (Korsch and Barnett), 707
Childhood and adolescence, severe acquired mitral stenosis in (Castle and Baylin), 404
early, head banging in (de Lissovoy), 803
Children with galactosemia, growth and development of, (Donnell, Collado, and Koch), 836
studies of incidence of carriers of enteropathogenic Escherichia coli in (Solomon, Weinstein, and Joress), 716
Chloramphenicol in premature infants, dosage of (Ziegra and Storm), 852
Cholesterol, lysolecithin and, in icterus neonatorum (Gotlieb, Pesach, and Rimon), 829
Chylous cysts of mesentery in infants (Stahl and Joy), 373
Clinical and epidemiologic background of Chagas' disease in United States. American trypanosomiasis (Woody and Woody), 568
Clinical pathological conference:
Generalized cytomegalic inclusion disease of newborn, 588
Neuronal degeneration after Compazine, 424
Postnecrotic scarring of liver, 126
Unidentified viral infection and encephalitis, 292
Whooping cough and adenovirus, 876
Comments on current literature:
Antihemophilic globulin levels in carriers of hemophilia A (Blattner), 298
Complications of viral hepatitis (Blattner), 596
Diarrhea caused by deficiency of sugar-splitting enzymes (Blattner), 883
Photic seizures—television-induced (Blattner), 746
Rabies infection transmitted by insectivorous bats: human case with virus isolation from spinal fluid during life (Blattner), 433
Recent findings concerning viremia in human subject (Blattner), 134
Compazine, neuronal degeneration after (CPC), 424
Complications in nephrotic syndrome, physiologic considerations concerning corticosteroid therapy and (Symposium) (Calcagno and Rubin), 686
of viral hepatitis (Blattner), 596
Congenital abnormalities of urinary system (Rubenstein, Meyer, and Bernstein), 356
aplasia or marked hypoplasia of myocardium of right ventricle (Uhl's anomaly), (Arcilla and Gasul), 381

Congenital—Cont'd
dextrocardia (Arcilla and Gasul), 39
(concluded) (Arcilla and Gasul), 251
Conjoined thoracopagus twins (Hill et al.), 59
Constrictive pericarditis, acute (Weis and Silber), 548
Convulsions in children following alcohol ingestion, hypoglycemia and (Cummins), 23
Correspondence, 140, 753
Corticosteroid therapy and complications in nephrotic syndrome, physiologic considerations concerning (Symposium) (Calcagno and Rubin), 686
Craniosynostosis involving the sagittal suture only: guilt by association? (Hemple et al.), 342
Crothers, Bronson, (1884-1959) (Byers), 438
Cyanosis, methylene blue induced, and acute hemolytic anemia complicating treatment of methemoglobinemia (Goluboff and Wheaton), 86
Cytomegalic inclusion disease, generalized, of newborn (CPC), 588
Cytomegaloviruses by children with generalized neoplastic disease, urinary excretion of (Hanshaw and Weller), 305
Cysts, chylous, of mesentary in infants (Stahl and Joy), 373

D

Deficiency of sugar-splitting enzymes, diarrhea caused by (Blattner), 883
Deficit, neurological, programing for children with (Thelander and Phelps), 389
Degeneration, neuronal, after Compazine, (CPC), 424
Delayed maturation in development (Illingworth), 761
Dental caries experience of school children in Corvallis, Oregon, after 7 years of fluoridation of water (Tank and Storvick), 528
Development, delayed maturation in (Illingworth), 761
growth and, of children with galactosemia (Donnell, Collado, and Koch), 836
Dextrocardia, congenital (Arcilla and Gasul), 39
(concluded) (Arcilla and Gasul), 251
Dialysis, peritoneal, in salicylate intoxication (Etteldorf et al.), 226
Diamox in epilepsy (Chao and Plumb), 211
Diarrhea caused by deficiency of sugar-splitting enzymes (Blattner), 883
parenteral fluid therapy of, regimens reconciled (editorial), 144
severe, in infants, parenteral fluid regimens in treatment of, (Smith and Etteldorf), 1
Differentiation, growth and, in developing embryo (Winick), 519
Diffusion, lung, diffusing capacity of pulmonary membrane, and capillary blood volume (Bucci, Cook, and Barrie), 820
Disease, Chagas', current serologic studies in American trypanosomiasis (Woody, DeDianous, and Woody), 738
extracellular volume: structure and measurement and influence of age and (Cheek), 103
generalized cytomegalic inclusion, of newborn (CPC), 588
maple syrup urine (Lane), 80
Diseases associated with some newly described viruses (Florman), 286
Drainage, peritoneal, of subdural hematomas in infants (Collins and Pucci), 482
Drug-resistant organisms, initial tuberculous infection due to (Zitrin and Lincoln), 219

E

Ear studies in newborn infant (McLellan and Webb), 523
Edema, nephrotic, studies on pathogenesis of (Symposium) (Metcoff and Janeway), 640
Editor's column:
Adult problem—a pediatric challenge? (Glenn), 304
Enuresis problem in children (Hill), 889
Legal rights of the child (Toolan), 605
Parenteral fluid therapy of diarrhea: regimens reconciled (West), 144
Pediatric career, 147
Pediatric ethical question (Veeder), 604
Psychiatry and Tower of Babel (Veeder), 303
Revision of the National Board of Medical Examiners tests completed, 891
Susceptibility to rheumatic disease (Coburn), 448
Thoughts about pediatrics (Parmelee), 451
Electrolyte and proteins, metabolism of, with particular emphasis upon changes in renal hemodynamics and (Symposium) (Metcoff and Janeway), 640
Embryo, developing, relationship of growth and differentiation in (Winick), 519
Encephalitis, unidentified viral infection and (CPC), 292
Enteropathogenic Escherichia coli in pediatric population, studies of incidence of carriers of (Solomon, Weinstein, and Joress), 716
Enuresis (Bakwin), 806
problem in children (editorial), 889
Environment, atmospheric, effect, on premature infants (Silverman), 581
Enzymes, sugar-splitting, diarrhea caused by deficiency of (Blattner), 383
Epidemiologic, clinical and, background of Chagas' disease in United States. American trypanosomiasis (Woody and Woody), 568
Epidermal necrolysis, toxic (Frain-Bell and Koblenzer), 722
Epilepsy, Diamox in (Chao and Plumb), 211
Erythrocyte T_3 uptake in early infancy, neonatal thyroid function (Marks, Wolfson, and Klein), 32

Escherichia coli, enteropathogenic, incidence of carriers in pediatric population (Solomon, Weinstein, and Joress), 716
pathogenic, in tropical countries, problem of sending fecal specimens to laboratory for isolation of (Suprihatin and Joe), 100
Ethical question, a pediatric (editorial), 604
Euthyroid children with goiter, immunologic and thyroid function studies in (Leboeuf et al.), 477
Exchange, cation, resin therapy for hyperkalemia in infants and children (Fleisher), 486
transfusion in rabbits, experimental observations on cardiac arrhythmia during (Taylor et al.), 470
Excretion, urinary, of cytomegaloviruses by children with generalized neoplastic disease (Hanshaw and Weller), 305
Extracellular volume: structure and measurement and influence of age and disease (Cheek), 103

F

Failure, cardiac, in infancy (McCue and Young), 330
Favism in a nursing infant (Emanuel and Schoenfeld), 263
Fecal specimens to laboratory for isolation of pathogenic Escherichia coli in tropical countries, problem of sending (Suprihatin and Joe), 100
Feeding, high caloric, on growth of premature infants, effect of (Snyderman and Holt), 237
Fluid therapy, parenteral, of diarrhea; regimens reconciled (editorial), 144
Fluoridation of water, dental caries experience of school children in Corvallis, Oregon, after 7 years of (Tank and Storvick), 528
Fontanel bone, anterior (Brown), 800
bulging, a complication of tetracycline therapy in infants (Fields), 74
Function, immunologic and thyroid, studies in euthyroid children with goiter (Leboeuf et al.), 477
neonatal thyroid: erythrocyte T_3 uptake in early infancy (Marks, Wolfson, and Klein), 32
Furaltadone (Altafur), recovery from Salmonella meningitis after treatment with (Rosenthal, Neter, and Weppner), 377

G

Galactosemia, growth and development of children with (Donnell, Collado, and Koch), 836
Generalized cytomegalic inclusion disease of newborn (CPC), 588
Globulin, antihemophilic, levels in carriers of hemophilia A (Blattner), 298
Goiter, immunologic and thyroid function studies in euthyroid children with (Leboeuf et al.), 477
Griseofulvin therapy in tinea capitis (Alban), 367
Growth and development of children with galactosemia (Donnell, Collado, and Koch), 836
and differentiation in developing embryo, relationship of (Winick), 519
of premature infants, effect of high caloric feeding on (Snyderman and Holt), 237

H

Head banging in early childhood (de Lissovoy), 803
Hematomas, subdural, in infants, peritoneal drainage of (Collins and Pucci), 482
Hemochromatosis, cardiac complications of chronic, severe, refractory anemia with (Master et al.), 455
Hemodynamic findings, congenital aplasia or marked hypoplasia of myocardium of right ventricle (Uhl's anomaly) (Arcilla and Gasul), 381
Hemodynamics, renal, and metabolism of electrolyte and proteins, with particular emphasis upon changes in (Symposium) (Metcoff and Janeway), 640
Hemolytic anemia, acute, complicating treatment of methemoglobinemia, methylene blue induced cyanosis and (Goluboff and Wheaton), 86
Hemophilia A, antihemophilic globulin levels in carriers of (Blattner), 298
Hepatitis, viral, complications of (Blattner), 596
Herpes virus and cytomegalic inclusion virus (CPC), 588
High caloric feeding on growth of premature infants, effect of (Snyderman and Holt), 237
Histoplasma meningitis with amphotericin B, successful treatment of (Snyder and White), 554
Hospital admissions for pediatric accidents in Upper Assam (Foll), 93
Human subject, recent findings concerning viremia in (Blattner), 134
Hydrocephalus, arrested, what is (Schick and Matson), 791
5-Hydroxyindole metabolism in autistic and other mentally retarded children (Schain and Freedman), 315
Hypercalcemia, idiopathic, of infancy, cardiac findings in (Rashkind, Golinko, and Arcasoy), 464
Hyperkalemia in infants and children, cation exchange resin therapy for (Fleisher), 486
Hypoglycemia and convulsions in children following alcohol ingestion (Cummins), 23
recognition and investigation (Hartmann, Wohltmann, and Holowach), 864
Hypoplasia of myocardium of right ventricle (Uhl's anomaly), congenital aplasia or (Arcilla and Gasul), 381
Hypoprothrombinemia, "solubilized" vitamin K_1 (phytonadione), in neonatal (Shoshkes et al.), 27

I

Icterus neonatorum, role of lysolecithin and cholesterol in (Gotlieb, Pesach, and Rimon), 829
Immunization, neonatal, with triple antigen, response of infants to poliomyelitis immunization after (Gaisford, Feldman, and Perkins), 493
  poliomyelitis, after neonatal immunization with triple antigen, response of infants to (Gaisford, Feldman, and Perkins), 493
Immunologic and thyroid function studies in euthyroid children with goiter (Leboeuf et al.), 477
Incidence of carriers of enteropathogenic Escherichia coli in pediatric population (Solomon, Weinstein, and Joress), 716
Inclusion, generalized cytomegalic, disease of newborn (CPC), 588
Industrialized part of Africa, pediatrics in (Kahn), 277
Infancy, cardiac failure in (McCue and Young), 330
  idiopathic hypercalcemia of, cardiac findings of, 464
  neonatal thyroid function: erythrocyte T_3 uptake in early (Marks, Wolfson, and Klein), 32
  sickle cell anemia in (Haggard and Schneider), 785
Infant, favism in (Emanuel and Schoenfeld), 263
  newborn, ear studies in (McLellan and Webb), 523
  premature, effect of atmospheric environment on (Silverman), 581
Infantile beriberi, acute (Reid), 858
Infants, bulging fontanel: complication of tetracycline therapy in (Fields), 74
  chylous cysts of mesentery in (Stahl and Joy), 373
  parenteral fluid regimens in treatment of severe diarrhea in (Smith and Ettledorf), 1
  premature, dosage of chloramphenicol in (Ziegra and Storm), 852
    effect of high caloric feeding on growth of (Snyderman and Holt), 237
Infection, chemoprophylaxis of. I. Introduction and general principles, symposium on (Petersdorf), 149
  initial tuberculous, due to drug-resistant organisms (Zitrin and Lincoln), 219
  in susceptible individuals, protection against (Symposium) (Petersdorf, Browder, and Feinstein), 174
  unidentified viral, and encephalitis (CPC), 292
Infections by specific pathogens, use of antibiotics (Symposium) (Petersdorf and Woodward), 153
Influenza, Asian, vaccine administered by intradermal and subcutaneous routes, response of infants and children to (Klein and Huang), 312
Initial tuberculous infection due to drug-resistant organisms (Zitrin and Lincoln), 219
Insectivorous bats: rabies infection transmitted by, human case with virus isolation from spinal fluid during life (Blattner), 433
Intoxication, salicylate, peritoneal dialysis in (Etteldorf et al.), 226
Intracardiac myxoma involving right and left atria in young patient (Cumming and Finkel), 559
Intradermal and subcutaneous routes, response of infants and children to Asian influenza vaccine administered by (Klein and Huang), 312
Introduction and general principles. I. Symposium on chemoprophylaxis of infection (Petersdorf), 149
  symposium on nephrotic syndrome (Metcoff), 607
Isolation of pathogenic Escherichia coli in tropical countries, problem of sending fecal specimens to laboratory for (Suprihatin and Joe), 100
  virus, from spinal fluid during life, rabies infection transmitted by insectivorous bats (Blattner), 433

K

Kanamycin sulfate as therapeutic agent for infants and children (Yow and Tengg), 538
Kwashiorkor in Cape Town: background of patients and their progress after discharge (Moodie), 392

L

Laboratory for isolation of pathogenic Escherichia coli in tropical countries, problem of sending fecal specimens to (Suprihatin and Joe), 100
Legal rights of child (editorial), 605
Leukemia, chickenpox and (Pinkel), 729
Liver, postnecrotic scarring of (CPC), 126
Lung diffusion, diffusing capacity of pulmonary membrane, and capillary blood volume (Bucci, Cook, and Barrie), 820
Lysolecithin and cholesterol in icterus neonatorum, role of (Gotlieb, Pesach, and Rimon), 829

M

Male, Turner's syndrome in (Steiker et al.), 321
Maple syrup urine disease (Lane), 80
Mastocytosis, changing concepts concerning (Bigelow), 499
Maternal medication, effect on neonate and his behavior (Brazelton), 513
Maturation, delayed, in development (Illingworth), 761
Meconium peritonitis presenting as abdominal mass (Shurtleff), 267
Medical progress:
  Effect of atmospheric environment on premature infants (Silverman), 581
  Extracellular volume: its structure and measurement and influence of age and disease (Cheek), 103
  Recognition and investigation of hypoglycemia (Hartmann, Wohltmann, and Holowach), 864

Severe acquired mitral stenosis in childhood and adolescence (Castle and Baylin), 404
Some newly described viruses and diseases associated with them (Florman), 286
Medication, maternal, effect on neonate and his behavior (Brazelton), 513
Meningitis, Histoplasma, with amphotericin B, successful treatment of (Snyder and White), 554
Salmonella, recovery after treatment with furaltadone (Altafur) (Rosenthal, Neter, and Weppner), 377
Meningoencephalitis, viral (Middelkamp et al.), 205
Mentally retarded children, 5-hydroxyindole metabolism in autistic and (Schain and Freedman), 315
Mesentery, chylous cysts of, in infants (Stahl and Joy), 373
Metabolism of electrolyte and proteins, with particular emphasis upon changes in renal hemodynamics and (Symposium) (Metcoff and Janeway), 640
5-hydroxyindole, in autistic and other mentally retarded children, studies on (Schain and Freedman), 315
Methemoglobinemia, methylene blue induced cyanosis and acute hemolytic anemia complicating treatment of (Goluboff and Wheaton), 86
pyridium-induced (Sand and Edelmann), 845
Methylene blue induced cyanosis and acute hemolytic anemia complicating treatment of methemoglobinemia (Goluboff and Wheaton), 86
Mitral stenosis, severe acquired, in childhood and adolescence (Castle and Baylin), 404
Mycobacterial cervical adenitis in children (Davis and Comstock), 771
Myocardium of right ventricle, congenital aplasia or marked hypoplasia of (Uhl's anomaly) (Arcilla and Gasul), 381
Myxoma, intracardiac, involving right and left atria in young patient (Cumming and Finkel), 559

N

National Board of Medical Examiners tests completed, revision of (editorial), 891
Necrolysis, toxic epidermal (Frain-Bell and Koblenzer), 722
Neonatal hypoprothrombinemia, "solubilized" vitamin K_1 (phytonadione) in (Shoshkes et al.), 27
immunization with triple antigen, response of infants to poliomyelitis immunization after (Gaisford, Feldman, and Perkins), 493
thyroid function: erythrocyte T_3 uptake in early infancy (Marks, Wolfson, and Klein), 32
Neonate, psychophysiologic reactions in. I. (Brazelton), 508
II (Brazelton), 513
Neoplastic disease, generalized, urinary excretion of cytomegaloviruses by children with (Hanshaw and Weller), 305
Nephrosis, physician, family, and child with (Symposium) (Korsch and Barnett), 707
Nephrotic edema, studies on pathogenesis of (Symposium) (Metcoff and Janeway), 640
syndrome, pathogenesis of, considerations based on clinical and experimental studies (Symposium) (Heymann), 609
pathology of (Symposium) (Vernier, Worthen, and Good), 620
physiologic considerations concerning corticosteroid therapy and complications in (Symposium) (Calcagno and Rubin), 686
symposium on, introduction (Metcoff), 607
Nerve palsies, postinjection sciatic, in infants and children (Gilles and French), 195
Neurological deficit, programing for children with (Thelander and Phelps), 389
Neuronal degeneration after Compazine (CPC), 424
Newborn, generalized cytomegalic inclusion disease of (CPC), 588
infant, ear studies in (McLellan and Webb), 523
sleep patterns of (Parmelee, Schulz, and Disbrow), 241
News and notes, 141, 301, 446, 602, 755, 887
Nursing infant, favism in (Emanuel and Schoenfeld), 263

O

Outpatient department, evaluation of resident training (Ambuel), 272

P

Palsies, postinjection sciatic nerve, in infants and children (Gilles and French), 195
Parenteral fluid regimens in treatment of severe diarrhea in infants (Smith and Etteldorf), 1
Pathogenesis of nephrotic edema, studies on (Symposium) (Metcoff and Janeway), 640
syndrome: considerations based on clinical and experimental studies (Symposium) (Heymann), 609
Pathogens, specific, use of antibiotics to prevent infections by (Symposium) (Petersdorf and Woodward), 153
Pathology of nephrotic syndrome (Symposium) (Vernier, Worthen, and Good), 620
Pediatric accidents in Upper Assam, hospital admissions for (Foll), 93
career (editorial), 147
challenge, an adult problem (editorial), 304
ethical question (editorial), 604
Pediatric profiles:
Bronson Crothers (1884-1959) (Byers), 438
Sir Robert Hutchison, Bart. (1871-1960) (Moncrieff), 137
Pediatrics in an industrialized part of Africa (Kahn), 277
thoughts about (editorial), 451

Pericarditis, acute constrictive (Weis and Silber), 548
Peritoneal dialysis in salicylate intoxication (Etteldorf et al.), 226
drainage of subdural hematomas in infants (Collins and Pucci), 482
Peritonitis, meconium, presenting as abdominal mass (Shurtleff), 267
Phenylketonuria: some observations on reflex activity (French et al.), 17
Phonocardiographic features, radiographic and, severe acquired mitral stenosis in childhood and adolescence (Castle and Baylin), 404
Photic seizures—television-induced (Blattner), 746
Physician, family, and child with nephrosis (Symposium) (Korsch and Barnett), 707
Physiologic considerations concerning corticosteroid therapy and complications in nephrotic syndrome (Symposium) (Calcagno and Rubin), 686
Physiology, respiratory, in children (Bucci, Cook, and Barrie), 820
Phytonadione, "solubilized" vitamin K_1, in neonatal hypoprothrombinemia (Shoshkes et al.), 27
Poliomyelitis immunization after neonatal immunization with triple antigen, response of infants to (Gaisford, Feldman, and Perkins), 493
vaccine, Salk, unpredictability of antibody response of infants to injections of (Cramblett and Fomon), 779
Postinjection sciatic nerve palsies in infants and children (Gilles and French), 195
Postnecrotic scarring of liver (CPC), 126
Poststreptococcal sequelae and bacterial endocarditis, prophylaxis of (Symposium) (Feinstein, Petersdorf, and Browder), 164
Premature infant, effect of atmospheric environment on (Silverman), 581
infants, dosage of chloramphenicol in (Ziegra and Storm), 852
effect of high caloric feeding on growth of (Snyderman and Holt), 237
Programing for children with neurological deficit (Thelander and Phelps), 389
Prophylaxis of poststreptococcal sequelae and bacterial endocarditis (Symposium) (Feinstein, Petersdorf, and Browder), 164
Protection against infection in susceptible individuals (Symposium) (Petersdorf, Browder, and Feinstein), 174
Proteins, metabolism of electrolyte and, with particular emphasis upon changes in renal hemodynamics (Symposium) (Metcoff and Janeway), 640
Psychiatry and Tower of Babel (editorial), 303
Psychophysiologic reactions in neonate. I (Brazelton), 508
II (Brazelton), 513
Pulmonary capillary blood volume, diffusing capacity of pulmonary membrane, and total lung diffusion (Bucci, Cook, and Barrie), 820
Pulmonary—Cont'd
membrane, diffusing capacity of, total lung diffusion, and pulmonary capillary blood volume (Bucci, Cook, and Barrie), 820
Pyridium-induced methemoglobinemia (Sand and Edelmann), 845

R

Rabies infection transmitted by insectivorous bats: human case with virus isolation from spinal fluid during life (Blattner), 433
Radiographic and phonocardiographic features, severe acquired mitral stenosis in childhood and adolescence (Castle and Baylin), 404
Reactions, psychophysiologic, in neonate. I (Brazelton), 508
II (Brazelton), 513
Recovery from Salmonella meningitis after treatment with furaltadone (Altafur) (Rosenthal, Neter, and Weppner), 377
Reflex activity, phenylketonuria: some observations on (French et al.), 17
Regimens, parenteral fluid, in treatment of severe diarrhea in infants (Smith and Etteldorf), 1
reconciled, parenteral fluid therapy of diarrhea (editorial), 144
Renal hemodynamics and metabolism of electrolyte and proteins, with particular emphasis upon changes in (Symposium) (Metcoff and Janeway), 640
Resident training in outpatient department (Ambuel), 272
Resin, cation exchange, therapy for hyperkalemia in infants and children (Fleisher), 486
Respiratory physiology in children (Bucci, Cook, and Barrie), 820
Response, antibody, of infants to injections of Salk poliomyelitis vaccine, unpredictability of (Cramblett and Fomon), 779
Retarded children, mentally, studies on 5-hydroxyindole metabolism in (Schain and Freedman), 315
Rheumatic disease, susceptibility to (editorial), 448
Right ventricle, congenital aplasia or marked hypoplasia of myocardium of (Arcilla and Gasul), 381
Rights, legal, of child (editorial), 605
Rupture, spontaneous, of stomach (James), 849

S

Sagittal suture only, craniosynostosis involving (Hemple et al.), 342
Salicylate intoxication, peritoneal dialysis in (Etteldorf et al.), 226
Salk poliomyelitis vaccine, unpredictability of antibody response of infants to injections of (Cramblett and Fomon), 779
Salmonella meningitis, recovery after treatment with furaltadone (Altafur), (Rosenthal, Neter, and Weppner), 377
Scalded skin syndrome, toxic epidermal necrolysis (Frain-Bell and Koblenzer), 722

Scarring of liver, postnecrotic (CPC), 126
Sciatic nerve palsies, postinjection, in infants and children (Gilles and French), 195
Seizures, photic—television-induced (Blattner), 746
Sequelae, poststreptococcal, and bacterial endocarditis, prophylaxis of (Symposium) (Feinstein, Petersdorf, and Browder), 164
Serologic studies in Chagas' disease. American trypanosomiasis (Woody, DeDianous, and Woody), 738
Sickle cell anemia in first 2 years of life (Haggard and Schneider), 785
Sir Robert Hutchison, Bart. (1871-1960) (Moncrieff), 137
Skin, scalded, syndrome, toxic epidermal necrolysis (Frain-Bell and Koblenzer), 722
Sleep patterns of newborn (Parmelee, Schulz, and Disbrow), 241
"Solubilized" vitamin K_1 (phytonadione), in neonatal hypoprothrombinemia (Shoshkes et al.), 27
Soybean, anaphylaxis following ingestion of (Mortimer), 90
Specific pathogens, use of antibiotics to prevent infections by (Symposium) (Petersdorf and Woodward), 153
Specimens, fecal, to laboratory for isolation of pathogenic Escherichia coli in tropical countries, problem of sending (Suprihatin and Joe), 100
Spinal fluid during life, human case with virus isolation from, rabies infection transmitted by insectivorous bats (Blattner), 433
Spontaneous rupture of stomach (James), 849
Stenosis, mitral, severe acquired, in childhood and adolescence (Castle and Baylin), 404
Stomach, spontaneous rupture of (James), 849
Subcutaneous, intradermal and, routes, responses of infants and children to Asian influenza vaccine administered by (Klein and Huang), 312
Subdural hematomas in infants, peritoneal drainage of (Collins and Pucci), 482
Sugar-splitting enzymes, diarrhea caused by deficiency of (Blattner), 883
Susceptibility to rheumatic disease (editorial), 448
Susceptible patients, protection against infection in (Symposium) (Petersdorf, Browder, and Feinstein), 174
Suture, sagittal, only, craniosynostosis involving (Hemple et al.), 342
Symposium on chemoprophylaxis of infection. I. Introduction and general principles (Petersdorf), 149
  nephrotic syndrome: introduction (Metcoff), 607
Syndrome, nephrotic, pathology of (Symposium) (Vernier, Worthen, and Good), 620
  physiologic considerations concerning corticosteroid therapy and complications in (Symposium) (Calcagno and Rubin), 686
  symposium on, introduction (Metcoff), 607
Syndrome—Cont'd
  scalded skin, toxic epidermal necrolysis (Frain-Bell and Koblenzer), 722
  Turner's in male (Steiker et al.), 321
Syrup, maple, urine disease (Lane), 80
System, urinary, congenital abnormalities of (Rubenstein, Meyer, and Bernstein), 356

T

T_3 uptake, erythrocyte, in early infancy, neonatal thyroid function (Marks, Wolfson, and Klein), 32
Television-induced photic seizures (Blattner), 746
Tetracycline therapy in infants, bulging fontanel: a complication of (Fields), 74
Therapy, cation exchange resin, for hyperkalemia in infants and children (Fleisher), 486
  corticosteroid and complications in nephrotic syndrome, physiologic considerations concerning (Symposium) (Calcagno and Rubin), 686
  griseofulvin, in tinea capitis (Alban), 367
  tetracycline, in infants, bulging fontanel: complication of (Fields), 74
Thoracopagus twins, conjoined (Hill et al.), 59
Thoughts about pediatrics (editorial), 451
Thyroid function, neonatal: erythrocyte T_3 uptake in early infancy (Marks, Wolfson, and Klein), 32
  studies in euthyroid children with goiter, immunologic and (Leboeuf et al.), 477
Tinea capitis, griseofulvin therapy in (Alban), 367
Tongue, accidental isolated primary vaccinia of (Scott and Steigman), 77
Toxic epidermal necrolysis (Frain-Bell and Koblenzer), 722
Tower of Babel, psychiatry and (editorial), 303
Training, resident, in outpatient department, evaluation of (Ambuel), 272
Transfusion, exchange, in rabbits, experimental observations on cardiac arrhythmia during (Taylor et al.), 470
Treatment with furaltadone (Altafur), recovery from Salmonella meningitis after (Rosenthal, Neter, and Weppner), 377
  methemoglobinemia, methylene blue induced cyanosis and acute hemolytic anemia complicating (Goluboff and Wheaton), 86
  severe diarrhea in infant, parenteral fluid regimens in (Smith and Etteldorf), 1
  successful, of Histoplasma meningitis with amphotericin B (Snyder and White), 554
Triiodothyronine uptake, erythrocyte, in early infancy, neonatal thyroid function (Marks, Wolfson, and Klein), 32
Triple antigen, response of infants to poliomyelitis immunization after neonatal immunization with (Gaisford, Feldman, and Perkins), 493

Tropical countries, problem of sending fecal specimens to laboratory for isolation of pathogenic Escherichia coli in (Suprihatin and Joe), 100
Tropical pediatrics:
Acute infantile beriberi (Reid), 858
American trypanosomiasis. I. (Woody and Woody), 568
American trypanosomiasis. II. (Woody, DeDianous, and Woody), 738
Hospital admissions for pediatric accidents in Upper Assam (Foll), 93
Kwashiorkor in Cape Town: background of patients and their progress after discharge (Moodie), 392
Pediatrics in an industrialized part of Africa (Kahn), 277
Problem of sending fecal specimens to laboratory for isolation of pathogenic Escherichia coli in tropical countries (Suprihatin and Joe), 100
Trypanosomiasis, American. I. (Woody and Woody), 569
II (Woody, DeDianous, and Woody), 738
Tuberculous infection, initial, due to drug-resistant organisms (Zitrin and Lincoln), 219
Turner's syndrome in male (Steiker et al.), 321
Twins, conjoined thoracopagus (Hill et al.), 59
Tympanic membrane, age of spontaneous visibility of auditory canal and (McLellan and Webb), 523

U

Uhl's anomaly, congenital aplasia or marked hypoplasia of myocardium of right ventricle (Arcilla and Gasul), 381
Unidentified viral infection and encephalitis (CPC), 292
Upper Assam, hospital admissions for pediatric accidents in (Foll), 93
Urinary excretion of cytomegaloviruses by children with generalized neoplastic disease (Hanshaw and Weller), 305
system, congenital abnormalities of (Rubenstein, Meyer, and Bernstein), 356
Urine, maple syrup disease (Lane), 80

V

Vaccine, Asian influenza, administered by intradermal and subcutaneous routes, response of infants and children to (Klein and Huang), 312
poliomyelitis, Salk, unpredictability of antibody response of infants to injections of (Cramblett and Fomon), 779
Vaccinia, accidental isolated primary, of tongue (Scott and Steigman), 77
Ventricle, right, congenital aplasia or marked hypoplasia of myocardium of (Arcilla and Gasul), 381
Viral hepatitis, complications of (Blattner), 596
infection, unidentified, with encephalitis (CPC), 292
meningoencephalitis (Middelkamp et al.), 205
Viremia in human subject, recent findings concerning (Blattner), 134
Virus, cytomegalic inclusion, herpes virus and (CPC), 588
herpes, and cytomegalic inclusion virus (CPC), 588
isolation from spinal fluid during life, human case with, rabies infection transmitted by insectivorous bats (Blattner), 433
Viruses, some newly described, and diseases associated with (Florman), 286
Visibility, spontaneous, of auditory canal and tympanic membrane (McLellan and Webb), 523
Vitamin K_1 (phytonadione), "solubilized," in neonatal hypoprothrombinemia (Shoshkes et al.), 27
Volume, extracellular, structure and measurement and influence of age and disease (Cheek), 103

W

Whooping cough and adenovirus (CPC), 876

610.5
J86
F37

Copy 2

THE UNIVERSITY OF MICHIGAN
MAY 31 1961
MEDICAL LIBRARY

Index Number

THE JOURNAL OF PEDIATRICS

Volume 58 **JUNE 1961** *Number* 6

In this issue

Delayed maturation in development
R. S. Illingworth, M.D. (Leeds), F.R.C.P., D.P.H., D.C.H.

Mycobacterial cervical adenitis
Starkey D. Davis, M.D., and George W. Comstock, M.D.

Antibody response to Salk vaccine
Henry G. Cramblett, M.D., and Samuel J. Fomon, M.D.

Sickle cell anemia in first 2 years
Mary Ellen Haggard, M.D., and Rose G. Schneider, Ph.D.

Arrested hydrocephalus
Robert W. Schick, M.D., and Donald D. Matson, M.D.

Anterior fontanel bone
Webster H. Brown, M.D.

Head banging in early childhood
Vladimir de Lissovoy, Ph.D.

Enuresis
Harry Bakwin, M.D.

Respiratory physiology
Giovanni Bucci, M.D., Charles D. Cook, M.D., and Herbert Barrie, M.D.

Lysolecithin and cholesterol in icterus neonatorum
A. Gotlieb, M.D., J. Pesach, and A. Rimon, Ph.D.

Development of children with galactosemia
George N. Donnell, M.D., Manuel Collado, M.D., and Richard Koch, M.D.

Pyridium-induced methemoglobinemia
Richard E. Sand, M.D., and Chester M. Edelmann, Jr., M.D.

Spontaneous rupture of stomach
David H. James, Jr., M.D.

Chloramphenicol in premature infants
Sumner Root Ziegra, M.D., and Robert R. Storm, B.A.

Tropical pediatrics: Acute infantile beriberi
D. H. S. Reid, M.D., Ch.B., Captain, R.A.M.C.

Medical progress: Hypoglycemia
Alexis F. Hartmann, Sr., M.D., Hulda J. Wohltmann, M.D., and Jean Holowach, M.D.

Comments on current literature: Diarrhea caused by deficiency of sugar-splitting enzymes

A Complete Table of Contents is listed on page 1

The C. V. Mosby Company
3207 Washington Boulevard, St. Louis 3, Missouri

TO CONTROL VOMITING IN CHILDREN

Tigan is so safe it can be prescribed with complete confidence for the routine control of nausea and vomiting in pediatric practice. Tigan is as effective as the phenothiazines in antiemetic potency while avoiding the risk of extrapyramidal convulsive syndrome which may occasionally result from the use of phenothiazines in children.* And, unlike the antihistamines, Tigan will not encumber the child's normal activities with lethargy or sleepiness. Particularly useful in children: Tigan suppositories — when oral administration is not feasible.

*S. Q. Conlan, GP, 21:136, 1960.

Supplied: Tigan Suppositories–200 mg, boxes of 6.

Consult literature and dosage information, available on request, before prescribing.

The Tigan Bibliography: 1. I. Roseff, W. B. Abrams, J. Kaufman, L. Goldman and A. Bernstein, J. Newark Beth Israel Hosp., 9:189, 1958. 2. W. Schallek, C. A. Heise, E. F. Keith and R. P. Bogdon, J. Pharmacol. & Exper. Therap., 126:270, 1959. 3. W. B. Abrams, I. Roseff, J. Kaufman, L. M. Goldman and A. Bernstein, New York J. Med., 59:4217, 1959. 4. O. W. Davie, Clin. Med., 7:43, 1960. 5. L. A. Nathan, Curr. Therap. Res., 2:6, 1960. 6. Council on Drugs, New and Nonofficial Drugs, J.A.M.A., 172:1038, 1960. 7. O. L. Davidson, J. Tennessee M.A., 53:140, 1960. 8. O. Brandman, Gastroenterology, 38:775, 1960. 9. A. I. Kolodny, Am. J. M. Sc., 239:682, 1960. 10. F. Cassace, Colorado GP, 2:5, 1960.

ROCHE LABORATORIES

Division of Hoffmann-La Roche Inc.

TIGAN® Hydrochloride
4-[2-dimethylaminoethoxy]-benzyl 2-thienyl ketone hydrochloride

Tigan SUPPOSITORIES

June,

THE JOURNAL OF PEDIATRICS

Contents JUNE 1961

Delayed maturation in development 761
R. S. Illingworth, M.D. (Leeds), F.R.C.P., D.P.H., D.C.H., Sheffield, England

Mycobacterial cervical adenitis in children 771
Starkey D. Davis, M.D., and George W. Comstock, M.D., Columbus, Ga.

Unpredictability of antibody response of infants to injections of Salk poliomyelitis vaccine 779
Henry G. Cramblett, M.D., and Samuel J. Fomon, M.D., Winston-Salem, N. C.

Sickle cell anemia in the first 2 years of life 785
Mary Ellen Haggard, M.D., and Rose G. Schneider, Ph.D., Galveston, Texas

What is arrested hydrocephalus? 791
Robert W. Schick, M.D., and Donald D. Matson, M.D., Boston, Mass.

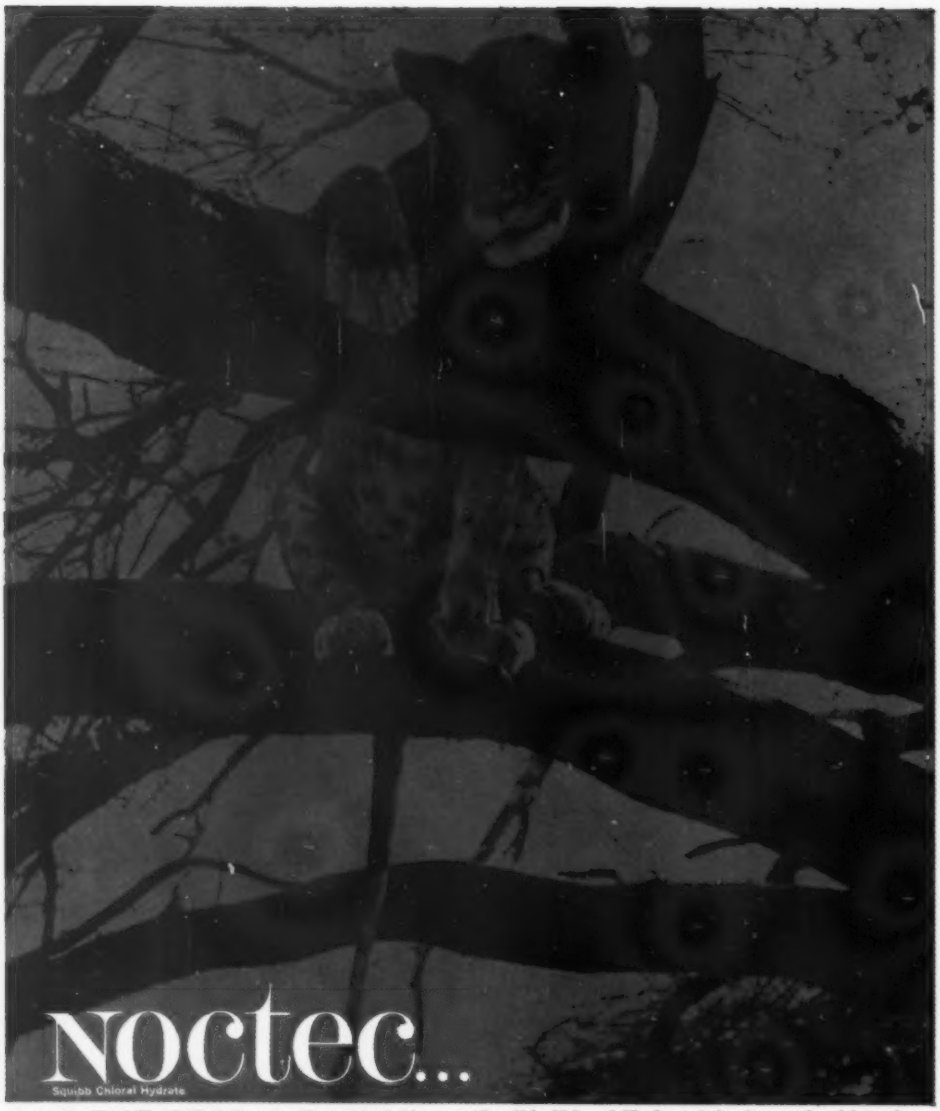
Anterior fontanel bone 800
Webster H. Brown, M.D., Baltimore, Md.

Head banging in early childhood 803
Vladimir de Lissovoy, Ph.D., University Park, Pa.

Enuresis in children 806
Harry Bakwin, M.D., New York, N. Y.

Studies of respiratory physiology in children 820
V. Total lung diffusion, diffusing capacity of pulmonary membrane, and pulmonary capillary blood volume in normal subjects from 7 to 40 years of age
Giovanni Bucci, M.D., Charles D. Cook, M.D., and Herbert Barrie, M.D. With the technical assistance of Joanna F. Hamann, Boston, Mass.

Continued on page 3



AND THE REST IS EASY! Noctec (Squibb Chloral Hydrate) invites refreshing sleep—gently, safely. Virtually free of side effects (including preliminary excitement or resultant "hangover" commonly observed with barbiturates), Noctec is conservative sleep therapy for patients of all ages. In recommended doses, Noctec may also be prescribed when heart disease or other illness is present • in psychiatric complications • during the first stage of labor • for pre- and postoperative sedation.

Dosage: Adults—1 or 2 500 mg. (7½ gr.) capsules or 1 or 2 teaspoonfuls of Noctec Syrup 15 to 30 minutes before bedtime. Children—for hypnosis—25 mg. per lb. of body weight; for sedation, 5 to 10 mg. per lb. of body weight.

Supply: 500 mg. (7½ gr.) and 250 mg. (3¾ gr.) capsules. Syrup, 500 mg., (7½ gr.) per 5 cc. teaspoonful.

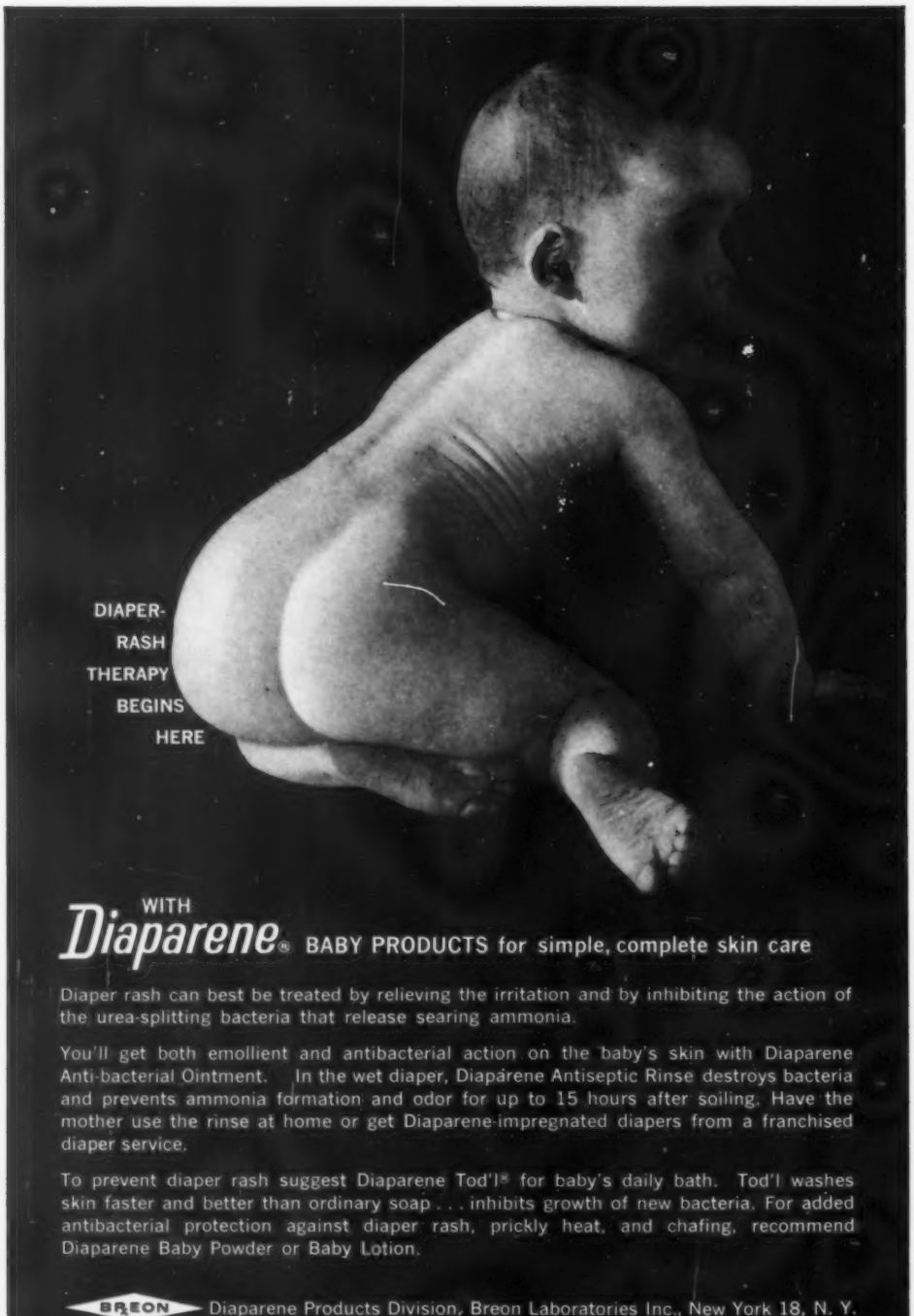
'Noctec'® is a Squibb trademark.

For full information, see your Squibb Product Reference or Product Brief.

SQUIBB
Squibb Quality—the Priceless Ingredient

CONTENTS *Continued*

	The role of lysolecithin and cholesterol in icterus neonatorum *A. Gotlieb, M.D., J. Pesach, and A. Rimon, Ph.D., Tel-Aviv, Israel*	829
	Growth and development of children with galactosemia *George N. Donnell, M.D., Manuel Collado, M.D., and Richard Koch, M.D., Los Angeles, Calif.*	836
	Pyridium-induced methemoglobinemia *Richard E. Sand, M.D., and Chester M. Edelmann, Jr., M.D., Portsmouth, Va.*	845
	Spontaneous rupture of the stomach *David H. James, Jr., M.D., West Memphis, Ark.*	849
	Dosage of chloramphenicol in premature infants *Sumner Root Ziegra, M.D., and Robert R. Storm, B.A., Brooklyn, N. Y.*	852
Tropical pediatrics	**Acute infantile beriberi** *D. H. S. Reid, M.B., Ch.B., Captain, R.A.M.C.*	858
Medical progress	**Recognition and investigation of hypoglycemia** *Alexis F. Hartmann, Sr., M.D., Hulda J. Wohltmann, M.D., and Jean Holowach, M.D., St. Louis, Mo.*	864
Clinical pathological conference	**The Children's Hospital Medical Center, Boston, Mass.**	876
Comments on current literature	**Diarrhea caused by deficiency of sugar-splitting enzymes** *Russell J. Blattner, M.D., Houston, Texas*	883
Books	**Books**	886
News and notes	**News and notes**	887
Editor's column	**The enuresis problem in children**	889
	Revision of the National Board of Medical Examiners tests completed	891
Index	**Index**	895



WITH
Diaparene® BABY PRODUCTS for simple, complete skin care

Diaper rash can best be treated by relieving the irritation and by inhibiting the action of the urea-splitting bacteria that release searing ammonia.

You'll get both emollient and antibacterial action on the baby's skin with Diaparene Anti-bacterial Ointment. In the wet diaper, Diaparene Antiseptic Rinse destroys bacteria and prevents ammonia formation and odor for up to 15 hours after soiling. Have the mother use the rinse at home or get Diaparene-impregnated diapers from a franchised diaper service.

To prevent diaper rash suggest Diaparene Tod'l® for baby's daily bath. Tod'l washes skin faster and better than ordinary soap . . . inhibits growth of new bacteria. For added antibacterial protection against diaper rash, prickly heat, and chafing, recommend Diaparene Baby Powder or Baby Lotion.

BREON Diaparene Products Division, Breon Laboratories Inc., New York 18, N. Y.
Subsidiary of Sterling Drug Inc.

THE JOURNAL OF PEDIATRICS

Editor WALDO E. NELSON
Philadelphia

Editorial board

HARRY BAKWIN
New York

RUSSELL J. BLATTNER
Houston

A. LAWRENCE CHUTE
Toronto

STEWART H. CLIFFORD
Boston

CHARLES DAVENPORT COOK
Boston

ROBERT E. COOKE
Baltimore

JAMES N. ETTELDORF
Memphis

ALEXIS F. HARTMANN
St. Louis

ALLAN J. HILL, JR.
Portland

LEE FORREST HILL
Des Moines

WALLACE W. MC CRORY
Iowa City

CARL H. SMITH
New York

CLARK D. WEST
Cincinnati

Contributing editors

SIDNEY FARBER
Boston

D. B. JELLIFFE
Uganda

GORDON VAWTER
Boston

Editor emeritus BORDEN S. VEEDER
St. Louis

Vol. 58, No. 6, June, 1961

The Journal of Pediatrics is published monthly by The C. V. Mosby Company, 3207 Washington Blvd., St. Louis 3, Mo. Subscription rates: United States, its Possessions, and Canada $12.00; Latin America and Spain $13.50; Other Countries $14.50. Students, interns, and resident physicians: United States, its Possessions, and Canada $7.20; Latin America and Spain $8.70; Other Countries $9.70. Single copies, $2.00 postpaid. Second class postage paid at St. Louis, Mo. Printed in the U. S. A.

Copyright © 1961 by The C. V. Mosby Company.

*As the greatest dental benefits of Sodium Fluoride are derived during infancy and early childhood:**

PEDIATRIC VITAMINS
PLUS SODIUM FLUORIDE

provide
proper
nutritional
support
plus
prophylaxis
against
future
dental
caries

FUNDAMENTAL VITAMINS PLUS SODIUM FLUORIDE

Funda-Vite® (F)

PEDIATRIC DROPS

Each 0.6 ml. provides, 400 U.S.P. units vitamin D, 30 mg. vitamin C and 0.5 mg. fluorine (as sodium fluoride). *Available in 30 ml. and 50 ml. bottles with calibrated droppers.*

MULTIPLE VITAMINS PLUS SODIUM FLUORIDE

Quanti-Vite™ (F)

PEDIATRIC DROPS

Each 0.6 ml. provides, 3,000 U.S.P. units vitamin A, 400 U.S.P. units vitamin D, 60 mg. vitamin C, 1 mg. vitamin B_1, 1.2 mg. vitamin B_2, 1 mg. vitamin B_6, 10 mg. niacinamide and 0.5 mg. fluorine (as sodium fluoride). *Available in 50 ml. bottles with calibrated droppers.*

AVAILABLE ON PRESCRIPTION ONLY
CONTRAINDICATED IN COMMUNITIES WITH FLUORIDATED DRINKING WATER.

*Council on Dental Therapeutics: Prescribing Supplements of Dietary Fluorides, J. Am. Dental Assoc. 56:589 (April) 1958.

* **NOTE:**
CONTINUE VITAMIN-FLUORIDE SUPPLEMENTS DURING THE SUMMER

Daily administrations of Funda-Vite(F) or Quanti-Vite(F) should be consistent and continuous if substantial dental benefits are to be anticipated.

HOYT

SAMPLES AND LITERATURE — Write Medical Department
HOYT PHARMACEUTICAL CORP., NEWTON 58, MASSACHUSETTS
PIONEERS IN PEDIATRIC VITAMIN-FLUORIDE SUPPLEMENTS

THE JOURNAL OF PEDIATRICS

Editor
Waldo E. Nelson, M.D.
2600 N. Lawrence Street
Philadelphia 33, Pa.

Publisher
The C. V. Mosby Company
3207 Washington Blvd.
St. Louis 3, Mo., U. S. A.

Editorial communications

The Journal of Pediatrics publishes articles on original research and clinical observations and reviews of pediatric subjects and related fields.

All manuscripts and editorial correspondence, except manuscripts on tropical pediatrics, should be submitted to the Editor, Waldo E. Nelson, M.D., 2600 North Lawrence Street, Philadelphia 33, Pa. Articles dealing with tropical pediatrics should be sent to D. B. Jelliffe, M.D., Makerere College Medical School, University College of East Africa, P. O. Box 2072, Kampala, Uganda, East Africa.

Articles are accepted for publication with the stipulation that they are submitted solely to The Journal of Pediatrics, and are subject to editorial revision. Neither the editor nor the publisher accepts responsibility for the views and statements of the authors. Manuscripts should be submitted by the head of the department in which the work was done or accompanied by a letter of approval. Galley proof will be sent to the senior author.

Preparation of manuscripts. Manuscripts should be typewritten on one side of the paper, double-spaced with liberal margins. By submitting articles in duplicate, editorial decision on the paper can be more prompt. The author should keep one carbon copy.

Academic titles for each author should be included.

References should be placed at the end of the article on a separate page; they should be numbered in the order in which they appear in the paper, and should conform to the style of the Quarterly Cumulative Index Medicus, i.e., author's last name, initials, title of article in original language, periodical (abbreviated and punctuated according to Q.C.I.M. usage), volume number, first and last page of article, and year of publication. References to books should include, in the following order, author, title, edition, city and year of publication, and publisher.

Illustrations. Illustrations accompanying manuscripts should be unmounted, numbered, and marked lightly on the back with the author's name. Legends should be typed on a separate sheet. Authors should indicate in the manuscript the appropriate positions of tables and illustrations.

A reasonable number of halftone illustrations will be reproduced free of cost to the author, but special arrangements must be made with the editor for color plates, elaborate tables, or an extra large number of illustrations. Copy for zinc cuts, such as pen drawing and charts, must be drawn in India ink and lettered in India ink or black typewriter ribbon. Only good glossy photographic prints and original drawings should be supplied for halftone work.

For illustrations showing recognizable faces, the author should enclose with his paper a letter of permission from the person, if an adult, or from the parent or guardian, if a child, or a statement that such permission has been obtained. For illustrations published in other publications, the author should include letters of permission for publication from the author and original publisher or a statement that such permission has been obtained.

Books for review. Books and monographs, native and foreign, will be reviewed depending on their interest and value to subscribers. No acknowledgment will be made of books received. Books may be sent to the Editor.

Letters to the Editor and news items. Concise, informative correspondence and announcements may be sent to the Editor for publication. Interesting letters, or portions of them, will be published, but unpublished letters will not be returned.

Business communications

Business communications. All communications in regard to advertising, subscriptions, change of address, etc., should be addressed to the Publishers, The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis 3, Missouri.

Subscription rates. United States, its Possessions, and Canada $12.00; Latin America and Spain $13.50; Other Countries $14.50. Students, interns, and resident physicians: United States, its Possessions, and Canada $7.20; Latin America and Spain $8.70; Other Countries $9.70. Single copies, $2.00 postpaid. Remittances for subscriptions should be made by check, draft, post office or express money order, payable to this Journal.

Change of address notice. Six weeks' notice is required to effect a change of address. Kindly give the exact name under which a subscription is entered and the full form of both old and new addresses, including the post office zone number.

Advertisements. Only articles of known scientific value will be given space. Forms close first day of month preceding date of issue. Advertising rates and page sizes on application.

Bound volumes. Publishers' Authorized Bindery Service, 430 West Erie Street, Chicago 10, Illinois, will quote prices for binding complete volumes in permanent buckram.

Reprints. Reprints of articles must be ordered directly through the Publishers, The C. V. Mosby Company, 3207 Washington Boulevard, St. Louis 3, Missouri, who will send their schedule of prices. Individual reprints of an article must be obtained through the author.

Published monthly.
Subscriptions may begin at any time.

NEW
pleasant
tasting
CHERRY
FLAVORED

for the asthmatic child

BRONKOTAB® ELIXIR

**Produces bronchodilation...
Overcomes associated anxiety...
AND provides the advantages of
an antihistamine and expectorant**

In a convenient dosage form for pediatrics, this pleasant-tasting, fast-acting preparation is the **only** elixir which provides **five** proven therapeutic agents for the comprehensive control and prophylactic maintenance of the asthmatic pediatric patient.

Dosage: Each 5 cc. (tsp.) BRONKOTAB ELIXIR contains:

1. Ephedrine Sulphate 12 mg.—for decongestion and relief of bronchospasm
2. Theophylline 15 mg.—for reducing local edema
3. Phenobarbital 4 mg.—for mild sedation
4. Glyceryl Guaiacolate 50 mg.—for effective expectorant action
5. Chlorpheniramine Maleate 1 mg.—for treatment of associated allergic complications

BRONKOTAB ELIXIR CLEARS AND DILATES THE BRONCHIAL TREE WITH FEW, IF ANY, SIDE EFFECTS

Adults 2 tsp. q.i.d.
Children over six: one-half adult dose.
Children under six: as directed by physician.

BREON

Rx Products Division
BREON LABORATORIES Inc., New York 18, N. Y.

THE JOURNAL OF PEDIATRICS

Articles to appear in early issues

A case of hemangioma with thrombocytopenia in the newborn infant treated by total excision
Joseph T. Inglefield, Jr., Captain, MC, USA, Patrick D. Tisdale, Captain, MC, USA, and John P. Fairchild, Lieutenant Colonel, MC, USA

The protein allowance in infancy and childhood
Joseph A. Johnston, M.D., Michael James Sweeney, M.D., Richard C. Brown, M.D., John W. Maroney, M.D., and Gordon Manson, M.D., Detroit, Mich.

Thyroid enlargement probably induced by cobalt
John L. Chamberlain, III, M.D., Nashville, Tenn.

"Diaper rash," a diagnostic anachronism
Philip J. Kozinn, M.D., Claire L. Taschdjian, B.Sc., M.S. (Ed.), and James J. Burchall, M.A., Brooklyn, N. Y.

A case of hypersensitivity to para-aminosalicylic acid in a child
Garry M. Kneebone, M.B., B.S., M.R.A.C.P., North Adelaide, South Australia

Magnesium balance studies in marasmic kwashiorkor
R. D. Montgomery, M.B., B.Chir., M.R.C.P., M.R.C.P.E., Kingston, Jamaica

Activity of acid phosphatase in the cerebrospinal fluid of children
Zvi Laron, M.D., and Avivah Kowadlo, B.Sc., Petah Tikva, Israel

Evaluation of transaminase activity in the cerebrospinal fluid in paralytic poliomyelitis
A. S. Abbassy, M.D., and M. H. Aboulwafa, Ph.D., Alexandria, Egypt, U.A.R.

Should infantile umbilical hernias be treated with navel emplastra
Fritz Karlstrom, Karlstad, Sweden

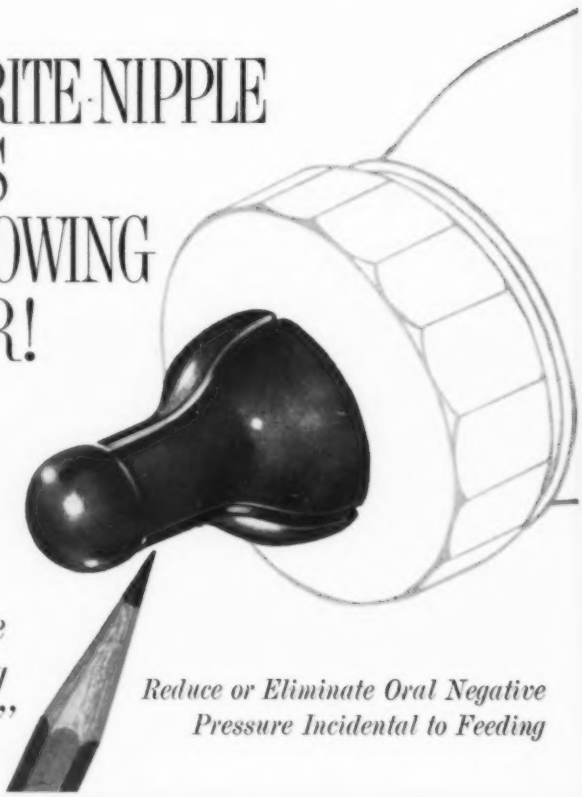
The investigation of a patient with hyperlipemia, hypokalemia, and tetany
Donald B. Cheek, M.D., D.Sc., M. J. Robinson, M.D., M.R.A.C.P., and F. D. Collins, Ph.D., Melbourne, Australia

Pulmonary resections in tuberculous children
Raúl Matte, M.D., Sergio Ibañez, M.D., and Helmut Jaeger, M.D., Santiago, Chile

Severe infections in children due to rare gram-negative bacilli (Mima polymorpha and Bacillus anitratum)
Mercedes Vda. de Torregrosa, Ph.D., and Antonio Ortiz, M.D., Santurce, Puerto Rico

Acute and chronic hypervitaminosis in a 4-month-old infant
William K. Woodard, M.D., Leroy J. Miller, M.D., and Omar Legant, M.D., Albuquerque, N. Mex.

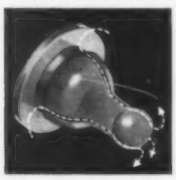
NEW FEED-RITE-NIPPLE MAKES SWALLOWING EASIER!



Exclusive "Breathing Channels"

Reduce or Eliminate Oral Negative Pressure Incidental to Feeding

The new Feed-Rite Nipple eliminates the problem of oral vacuum build-up. *Three* "breathing channels" enable the infant to *breathe as he feeds,* making possible a natural, *uninterrupted* swallowing action. Aerophagia is reduced . . . less bubbling is required.



The nipple, with its extra soft tip and base, adjusts to pressure changes which regulate the flow to a pace most comfortable for the infant. Special air vent helps keep formula flow constant . . . reduces nipple collapse.

FEED-RITE NIPPLE (Code #140)
NOW FEATURED ON ALL FEED-RITE NURSERS:

- NEW "THRIFTEE" FEED-RITE
- FEED-RITE PLASTIC
- FEED-RITE COLOR-SCALE
- FEED-RITE PYREX

"Twin Dimple" finger grips provide more secure handling. Economically priced along with other popular nursers.

DAVOL
RUBBER COMPANY
PROVIDENCE 2, R. I.

after eleven million treatment courses*... consistently broad antibacterial action

brand of nitrofurantoin

Furadantin® **through the years...consistently broad antibacterial action against urinary tract pathogens**—"It was interesting to observe that nitrofurantoin [FURADANTIN] showed a consistent in vitro effectiveness against the bacteria tested throughout the four year period, thus revealing negligible development of bacterial resistance, if any, through the years." Jolliff, C. R., et al.: Antibiot. Chemother. (Wash.) *10*:694, 1960.

*Conservative estimate based on the clinical use of FURADANTIN tablets and Oral Suspension since 1953.

rapid, safe control of infection throughout the urinary system

EATON LABORATORIES, Division of The Norwich Pharmacal Company, NORWICH, N.Y.

complete vitamin protection

...for engineers

or career women

the complete multivitamin in the pleasant tasting

SOFTAB® *form*

Mulvidren®

melts in the mouth
no water needed

or physicians

Stuart

THE STUART COMPANY • PASADENA, CALIFORNIA

or ball players

EACH TABLET CONTAINS:

VITAMINS

A	3,000 USP Units
D	1,000 USP Units
C	60 mg.
B_1	2 mg.
B_2	2 mg.
B_6	1 mg.
B_{12} in Lentz-12*	3 mg.
d-Calcium Pantothenate	3 mg.
Niacinamide	10 mg.

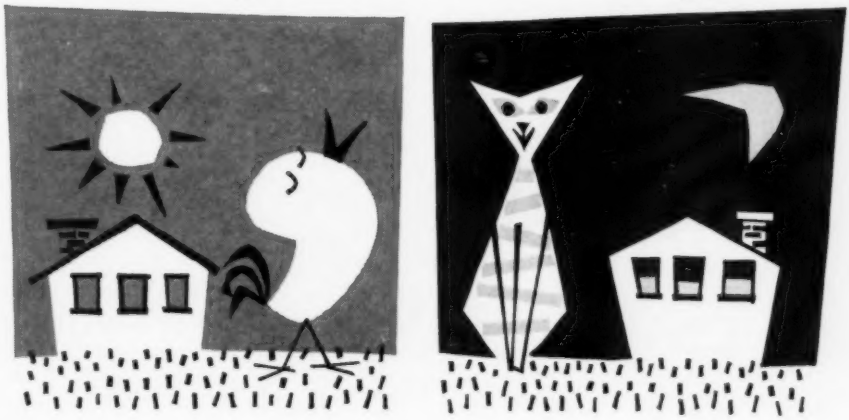
*Each Stuart Lentz-12 contains Vitamin B_{12} concentrate fermentation.

DOSAGE: 1 tablet daily or more as directed by physician.

AVAILABLE: Bottles of 50 & 100 tablets at all pharmacies.

Just one (1) capsule tranquilizes

all day or all night



Here is *single-capsule convenience* for your tense, nervous patients.

One capsule at breakfast relieves both mental and muscular tension *all through the day.*

One capsule in the evening provides restful sleep *all through the night.*

Prescribe Meprospan for safe and convenient *sustained* tranquilization . . . less trouble for your patient, less chance to forget medication.

Meprospan®-400

400 mg. Miltown® continuous release capsules

Supplied: *Meprospan-400,* each blue-topped, *continuous release* capsule contains 400 mg. Miltown (meprobamate, Wallace).

Also available: *Meprospan-200,* each yellow-topped, *continuous release* capsule contains 200 mg. Miltown.

WALLACE LABORATORIES/*Cranbury, N. J.*

CME-2192

* THE HEMATINIC WITH BUILT-IN NUTRITIONAL SUPPORT...

Women of menstrual age, many growing children, blood donors, geriatric patients and convalescents may need a hematinic . . . and all can benefit from Livitamin.

Livitamin offers the ideal formula to restore depleted iron reserves and give nutritional support—an important aspect of iron deficiency.

Iron in Livitamin is well absorbed and stored and well tolerated. B complex and other ingredients provide integrated nutritional support.

And Livitamin is a boon for your taste-fussy patients who *should* but *will not* take a hematinic.

LIVITAMIN®

. . . the hematinic with built-in nutritional support

FORMULA: Each fluidounce contains:

Iron peptonized (equiv. in elemental iron to 71 mg.)	420 mg.
Manganese citrate, soluble, N.F.	158 mg.
Thiamine hydrochloride	10 mg.
Riboflavin	10 mg.
Cobalamin	20 mcg.
Nicotinamide	50 mg.
Pyridoxine hydrochloride	1 mg.
Pantothenic acid	5 mg.
Liver fraction 1	2 Gm.
Rice bran extract	1 Gm.
Inositol	30 mg.
Choline	60 mg.

SUPPLIED: Liquid or capsule; also available as capsules, LIVITAMIN with Intrinsic Factor.

THE S. E. MASSENGILL COMPANY

Bristol, Tennessee • New York • Kansas City • San Francisco

STAPHCILLIN®

sodium methicillin (sodium dimethoxyphenyl penicillin)

FOR INJECTION

WIDESPREAD EXPERIENCE
IN RESISTANT 'STAPH' INFECTIONS
affirms the clinical significance of its unique property of virtually withstanding destruction by staphylococcal penicillinases[1-10]

WIDESPREAD EXPERIENCE
IN RESISTANT 'STAPH' INFECTIONS
has failed to show that Staphcillin is responsible for such toxic hazards as hearing impairment, renal damage, and blood dyscrasias characteristic of other antibiotics active against resistant staphylococci[4, 6, 9-14]

STAPHCILLIN... EFFECTIVE IN LIFE-THREATENING INFECTIONS CAUSED BY RESISTANT STAPHYLOCOCCI

Endocarditis, Septicemia, and Osteomyelitis

A 10-year-old boy was admitted to the hospital on August 11, 1960, acutely ill with high fever, and severe pain and swelling of the right knee, right thigh, and right elbow. Six days before, he had injured his right knee. On admission he had a systolic murmur. A short time later cardiac enlargement, slurring of speech, and ataxia of the right arm and leg developed. Blood culture revealed an abundant growth of coagulase-positive staphylococci; the same organisms were later identified in material drained from a large abscess surrounding part of the right femur, which was denuded of periosteum. The diagnosis was acute osteomyelitis, septicemia, and endocarditis caused by staphylococcal infection.

Over a period of 7 weeks, the following antibiotics were administered, but were discontinued because of inadequate improvement or toxicity: penicillin G, tetracycline, chloramphenicol, kanamycin, vancomycin, novobiocin, erythromycin, and ristocetin. Staphcillin was started on Sept. 29, 1960, 1 Gm. I.M., q. 6 h. (later reduced to 3 Gm. daily), and was given for 54 days. Shortly following initiation of this therapy, he became afebrile, and there was marked clinical improvement thereafter. There were no side effects from Staphcillin. As of March, 1961, he had had no recurrence of the infection, was afebrile, had gained weight and the ataxia and speech defect had almost disappeared. There was residual heart murmur. There were signs of osteomyelitis in the right femur on X-ray examination.

Evans, W. E.: Report to Dept. of Clin. Invest., Bristol Laboratories.

Empyema and Concurrent Pseudomonas Wound Infection

A 61-year-old male was injured in an automobile accident. He was operated upon for lacerations of the spleen, left diaphragm, pericardium, and left ventricle. He later developed a *Staph. aureus* empyema and a *Pseudomonas aeruginosa* abdominal wound infection. Chloramphenicol, erythromycin, and penicillin G were given, but discontinued because of inefficacy. Staphcillin was then administered, 2 Gm. q.i.d., for 30 days. Polymyxin B was administered concurrently for the Pseudomonas infection. The condition was improved, with apparent elimination of all infecting bacteria.

Hewitt, W. L.: Report to Dept. of Clin. Invest., Bristol Laboratories.

Pneumonia following Laparotomy

A 37-year-old man had a laparotomy performed at which acute pancreatitis was found. Postoperatively, he developed a bilateral staphylococcal bronchopneumonia. The organism was resistant to penicillin G. Before the laboratory tests were reported, he had been given massive doses of penicillin G for three days with no temperature response. Staphcillin was given intravenously, 1 Gm. every four hours, after which his temperature became normal in 48 hours, "and his clinical response was most gratifying."

Branch, A.; Rodger, K. C.; Lee, R. W., and Power, E. L.: Canad. M. A. J. 83:991 (Nov. 5) 1960.

Enterocolitis after Abdominal Surgery

A 65-year-old woman had profuse watery diarrhea 3 days after an abdominal operation. She became acutely ill, with a temperature of 103°F., tachycardia, leukocytosis, and fluid and electrolyte loss. Staphylococci in pure culture were identified on stool smear and culture. Tetracycline, which she had been receiving since operation, was discontinued, and Staphcillin (1.5 Gm. every 6 hours) administered parenterally. Within 48 hours she was afebrile, and the diarrhea had subsided. Staphylococci were eliminated from the stool. She received Staphcillin for 8 days, and was discharged as well on the 11th postoperative day.

Rutenburg, A. M.; Greenberg, H. L., and Schweinburg, F. B.: New Eng. J. Med. 263:1174 (Dec. 8) 1960.

SUMMARY OF SENSITIVITY STUDIES

Published data and reports to the Department of Clinical Investigation, Bristol Laboratories, concerning sensitivity of staphylococci to Staphcillin are summarized to date (March, 1961) as follows:

Total number of isolates 8,060

No. of isolates with a Minimum Inhibitory Concentration (M.I.C.) of 6.25 mcg./ml. or less (45 investigators) 8,052

No. of isolates with an M.I.C. of more than 6.25 mcg./ml. (4 investigators: Jevons, Rutenburg, Katz, Eichenwald) 8 (0.09%)

Blood levels well over 12 mcg./ml. are commonly reached for limited periods following the recommended I.M. or I.V. dosage of Staphcillin. Many infections caused by strains with an M.I.C. of 6.25 mcg./ml. have responded well to treatment with the recommended dosage. The rare incidence to date of strains of staphylococci with an M.I.C. of more than 6.25 mcg./ml. is shown in the above summary (0.09% of 8,060 isolates). Only in the future, following treatment of a sufficient number of such cases, can it be known whether they will respond to Staphcillin, and further, what the highest M.I.C. might be that is consistent with good clinical response.

THE ACTIVITY OF STAPHCILLIN IS VIRTUALLY UNAFFECTED BY STAPHYLOCOCCAL PENICILLINASES

The width of the clear zones around the sensitivity discs in Figs. 1 and 2 shows that Staphcillin acts against this resistant strain, and that penicillin G has little or no effect. The similarity in the width of the zones around Staphcillin discs in the light and heavy (increased concentration of penicillinase) inocula shows that penicillinase-producing staphylococci have virtually no effect on the antistaphylococcal activity of Staphcillin.

The clinical effectiveness of Staphcillin against penicillin G-resistant staphylococci is most probably related to Staphcillin's demonstrated resistance to destruction by penicillinase.

Penicillin G

Fig. 1
Light
Inoculum

STAPHCILLIN

Penicillin G

Fig. 2
Heavy
Inoculum

STAPHCILLIN

CONCURRENT ANTIBIOTIC THERAPY IN MIXED OR SUPERINFECTIONS

If mixed or superinfections due to Gram-negative organisms occur during Staphcillin therapy, appropriate measures should be taken. Clinical experience reported to the Department of Clinical Investigation, Bristol Laboratories can be summarized as follows: One or more antibiotics were employed concurrently with Staphcillin in the treatment of 88 patients. Of these, 73 improved, and there was no change in 5. There were 10 deaths, all of which were unrelated to antibiotic therapy; e.g., coronary thrombosis, pulmonary embolism, terminal carcinoma, etc. Among the antibiotics most commonly used with Staphcillin in this series of 88 patients were polymyxin, colistin, bacitracin, streptomycin, kanamycin and chloramphenicol.

STAPHCILLIN®

sodium methicillin (sodium dimethoxyphenyl penicillin)

FOR INJECTION

INDICATIONS: Staphcillin is recommended specifically for infections caused by strains of staphylococci susceptible to it and resistant to other penicillins. When laboratory sensitivity tests suggest that the staphylococci involved in an infection are susceptible to Staphcillin and to other antimicrobial agents, selection can be further guided by judgment of the nature of the infection, of the need for bactericidal action, and by considerations of comparative toxicity and convenience of administration.

SUCH INFECTIONS INCLUDE: *Skin and soft tissue infections:* cellulitis, wound infections, carbuncles, pyoderma, furunculosis, lymphangitis and lymphadenitis.

Respiratory infections: staphylococcal lobar pneumonia, bronchopneumonia, or lung abscess combined with indicated surgical treatment.

Other infections: staphylococcal septicemia, bacteremia, acute or subacute endocarditis, acute osteomyelitis and enterocolitis.

Infections due to penicillin-sensitive staphylococci, streptococci, pneumococci or gonococci, should be treated with Syncillin (potassium phenethicillin) or parenteral penicillin G, rather than with Staphcillin. Treponemal infections should be treated with parenteral penicillin G.

DOSAGE AND ADMINISTRATION: *Intramuscularly (deep intragluteal):* Adults—The usual dose is 1 Gm. every 4 to 6 hours. Infants and children—25 mg. per kg. of body weight (approximately 12 mg. per lb.) every 6 hours.

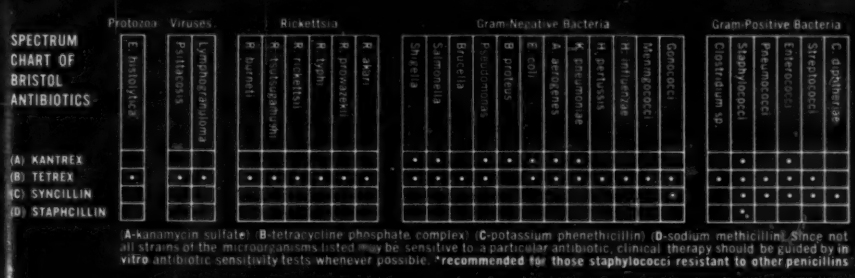
Intravenously: Adults—The usual dose is 1 Gm. every 6 hours, using 50 ml. of sterile saline solution at the rate of 10 ml. per minute.

PRECAUTIONS: Mild skin reactions, e.g., itching, papular eruptions, and erythema have occasionally been observed during treatment and after discontinuance of therapy. Patients with histories of hay fever, asthma, urticaria, and previous sensitivity to any penicillin are more likely to react to all penicillins, and the possibility of anaphylaxis should be kept in mind; epinephrine, antihistamines, and intravenous corticosteroids should be available for emergency treatment. Because of the virtually complete resistance of Staphcillin to destruction by penicillinase, parenteral *B. cereus* penicillinase may not be effective for treatment of allergic reactions. If superinfection by Gram-negative organisms or fungi occurs during Staphcillin therapy, appropriate measures should be taken.

SUPPLY: Staphcillin is available in 1 Gm. dry-filled vials, equivalent to 900 mg. of dimethoxyphenyl penicillin activity.

References: 1. Knox, R.: Brit. M.J. ii:690 (Sept. 3) 1960. 2. Stewart, G. T., *et al.*: Brit. M. J. ii:694 (Sept. 3) 1960. 3. Robinson, G. N., *et al.*: Lancet ii:564 (Sept. 10) 1960. 4. Rutenburg, A. M., *et al.*: New Eng. J. Med. **263**:1174 (Dec. 8) 1960. 5. Bunn, P. A., *et al.*: New York J. Med. **60**:3074 (Oct. 1) 1960. 6. Branch, A., *et al.*: Canad. M. A. J. **83**:991 (Nov. 5) 1960. 7. Gourevitch, A., *et al.*: Paper presented at Conference on Staphcillin in the Therapy of 'Resistant' Staphylococcal Disease, Sept. 7, 1960, State University of New York College of Medicine, Syracuse, New York. 8. Casson, K., and Lannon, J.: *vide supra.* 9. White, A. C., and Varga, D. T.: *vide supra.* 10. Knight, V., and Rifkind, D.: *vide supra.* 11. Douthwaite, A. H., and Trafford, J. A. P.: Brit. M. J. ii:687 (Sept. 3) 1960. 12. Pindell, M. H., *et al.*: *vide supra.* 13. Smith, I. M., and Counts, G. W.: *vide supra.* 14. Hewitt, W. L., *et al.*: *vide supra.*

PROFESSIONAL INFORMATION SERVICE: Whenever you desire additional information concerning clinical experience with Bristol antibiotics, you may avail yourself of the services of the Medical Department of Bristol Laboratories via a collect telephone call to New York, PLaza 7-8520, or by mail to the Medical Department, Bristol Laboratories, 630 Fifth Avenue, New York 20, N.Y.



(A-kanamycin sulfate) (B-tetracycline phosphate complex) (C-potassium phenethicillin) (D-sodium methicillin). Since not all strains of the microorganisms listed may be sensitive to a particular antibiotic, clinical therapy should be guided by *in vitro* antibiotic sensitivity tests whenever possible. *recommended for those staphylococci resistant to other penicillins

BRISTOL

BRISTOL LABORATORIES
SYRACUSE, N. Y.
Div. of Bristol-Myers Co.

when an antihistamine alone is not enough... 'ACTIFED'®

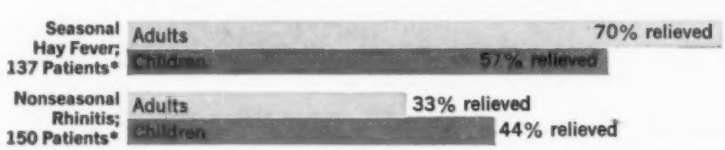
ANTIHISTAMINIC • DECONGESTANT

relieves the sneeze, wheeze, and other symptoms of HAY FEVER and ALLERGIES

- **effective in low dosage**
- **safe even for the youngest children**

Combining 'Actidil' (an antihistamine of unusually high potency) with 'Sudafed' (an orally effective nasal decongestant), 'ACTIFED' is "effective in a significant percentage of cases of seasonal and nonseasonal allergic rhinitis failing to respond to antihistamines alone."[1]

good to excellent results in rhinitis previously resistant to antihistamines



Prescribe safe 'ACTIFED' in tablet form or as a pleasant-tasting syrup:

Each scored tablet contains —

'Actidil'® brand Triprolidine Hydrochloride..... 2.5 mg.

'Sudafed'® brand Pseudoephedrine Hydrochloride.. 60 mg.

Each 5 cc. teaspoonful of the syrup contains —

'Actidil' brand Triprolidine Hydrochloride .....1.25 mg.

'Sudafed' brand Pseudoephedrine Hydrochloride. 30 mg.

DOSAGE: (may be given 3 times daily, or, because 'Actifed' has such a wide margin of safety, may be adjusted to provide optimal therapeutic effect in stubborn cases)

	Tablets	Syrup
Adults and children over 6 years	1	2 tsp.
Children 4 months to 6 years...	½	1 tsp.
Infants up to 4 months.....	—	½ tsp.

(While pseudoephedrine causes virtually no pressor effect in normotensive patients, it should be used with caution in hypertensives; and although triprolidine hydrochloride has an unusually low incidence of antihistaminic drowsiness, appropriate precautions should be observed.)

1. Feinberg, S. M., Feinberg, A. R., and Fisherman, E. W.: J. Indiana M. A. 52:2137 (Dec.) 1959.
*Adapted from authors' table.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York

citrus...
or non-citrus...

the same high natural vitamin C content in all 7 BiB juices

ACEROLA – EXCLUSIVE WITH BiB

Acerola juice is the richest known *natural* source of vitamin C.[1,2] All BiB juices are standardized to uniform vitamin C potency with Acerola juice. Whatever type you specify – citrus or non-citrus – less than one ounce provides the established Minimum Daily Requirement (10 mg.) of this essential vitamin for infants.

HYPOALLERGENIC – WELL TOLERATED

BiB juices are hypoallergenic and well tolerated. Acerola juice also is hypoallergenic. In a clinical study, "No reactions occurred from ingestion or from skin and intradermal tests with Acerola juice."[1] Tolerance and hypoallergenicity extend even to BiB Orange Juice by reducing to negligible quantities, the peel oil and seed protein content – factors largely responsible for sensitivities and poor tolerance to this fruit.[3]

EARLY TASTE-TRAINING

The seven BiB juices—Orange, Apple, White Grape, Pineapple, Prune-Orange, Orange-Apricot, and Tomato—provide valuable "taste-education" for the infant. BiB juice is ready for instant use—no squeezing, no defrosting or reconstitution—all mother does is open the container and it's ready for baby. "Micro-sized" for free flow through the bottle nipple – ideal for spoon or cup feeding too.

References: (1) Asenjo, C. F., and Freire de Guzman, A. R.: Science *103*:219 (Feb. 22) 1946. (2) Clein, N. W.: J. Pediat. *48*:140-145 (Feb.) 1956. (3) Ratner, B.; Untracht, S.; Malone, J., and Retsina, A.: J. Pediat. *43*:421 (Oct.) 1953. 40061

Edward Dalton Co.
A DIVISION OF
MEAD JOHNSON & COMPANY

Quality products from nutritional research

relieve

COLIC

when due to cow's milk allergy

specify

SOBEE®

Hypoallergenic soya formula

In a clinical study[1] of 206 milk-allergic infants, the "colicky" symptoms evident in 31% were promptly relieved when the infants were placed on a soya formula.

In another study[2] in which Sobee was fed to 24 infants allergic to cow's milk, "weight gain was satisfactory in all cases during the periods of observation."

Sobee was fed to 38 "colicky" milk-allergic infants;[3] 80% showed improvement.

1. Clein, N. W.: Pediat. Clin. North America, Nov., 1954, pp. 949-962.
2. Collins-Williams, C.: Canad. M.A.J. 75:934 (Dec. 1) 1956.
3. Kane, S.: Am. Pract. & Digest Treat. 8:65 (Jan.) 1957.

FOR PREVENTION: When allergic tendencies exist in parents or siblings, it is advisable to start the "potentially allergic" newborn on Sobee.

FOR DIAGNOSIS: If cow's milk allergy is suspected, a 24- to 48-hour trial period with Sobee often eliminates the need for an allergy study.

Acceptance of Sobee (liquid and "instant" powder) is excellent by both infants and mothers.[3] Sobee is simple to prepare . . . mothers do not have to add carbohydrate.

Mead Johnson Laboratories

Symbol of service in medicine

Today's little "limey"

needs a half barrel of orange juice his first two years

The British navy once conquered scurvy by giving its sailors lime juice to drink, but the problem has cropped up again today in an unexpected place: among infants! Noting a "recent and alarming prevalence" of infant scurvy, Whelan and co-workers state: "Emphatic and more specific advice from doctors concerning the value of orange juice in infant nutrition . . ." is needed.[1]

The infant should be given, during the first two years of his life, a total of 2,106 ounces—a half barrel—of orange juice. Whelan's group specifically recommends that . . . "Starting at two weeks of age, infants should receive, daily, one teaspoonful of orange juice (fresh, frozen or canned) diluted with an equal amount of boiled water. The amount should be increased by one teaspoonful of each, twice weekly, until the baby is receiving one ounce of orange juice and one ounce of water. Thereafter continue to increase the orange juice at the same rate until, at two months of age, the infant is receiving two ounces of orange juice (diluted with one ounce of water). At one year of age the orange juice should be increased to three or four ounces daily."

It's easy to be on the safe side. Check with each mother to be sure she's doing her part to help her infant empty that half barrel of orange juice he needs . . . Florida orange juice, of course! — fresh, frozen, canned, or in cartons.

1. Whelan, W. S.; Fraser, D.; Robertson, E. C., and Tomczak, H.: Canad. M.A.J. *78*:177 (Feb. 1) 1958.

©Florida Citrus Commission, Lakeland, Florida

vitamin K_1 and the disappearance of neonatal hemorrhage

"The widespread use of vitamin K in the newborn has change what was once a major pediatric problem . . . into a matter only academic interest."*

KONAKION provides the most efficient means of routine vitamin prophylaxis: faster rate of absorption than menadione or derivatives, wider margin of safety than vitamin K analogs, bo oral and parenteral dosages (the parenteral form is a fine aqu ous dispersion compatible with most intravenous vehicles). N a single case of kernicterus due to KONAKION has been reporte KONAKION is supplied in low-dosage ampuls, permitting econor cal one-time use.

A. J. Aballi, V. L. Banus, S. de Lamerens and S. Rozengvaig, J. Dis. Ch 97:524, 1959. And abstr. in J.A.M.A., 170:2249, 1959 and Nutrition Re 17:229, 1959.

Capsules — 5 mg. Ampuls — 1 mg 0.5 cc, 10 mg 1.0 cc, 25 mg 2.5

KONAKION

brand of vitamin K_1

STOP BLEEDING . . . SAFELY

ROCHE LABORATORIES
Division of Hoffmann-La Roche Inc. • Nutley 10, New Jersey

how would you design a tranquilizer specifically for children?

wouldn't you want it to be:

see how closely these ATARAX advantages meet your standards:

efficacious

"... Atarax appeared to reduce anxiety and restlessness, improve sleep patterns and make the child more amenable to the development of new patterns of behavior...."[1]

remarkably well tolerated

"The investigators were impressed with the lack of toxicity and minimal side effects which were observed even after long-term use."[2]

palatable

Delicious ATARAX syrup pleases even the balkiest patient.

Nor is that all ATARAX has to offer. In the allergic child, ATARAX offers added antihistaminic action to help control asthma and urticaria.[3] In fact, though outstandingly useful in children,[1-4] ATARAX equally well meets the needs of the elderly, and of the tense working adult (it calms, seldom impairing mental acuity). Why not extend its benefits to *all* your tense and anxious patients?

Dosage: For children: under 6 years, 50 mg. daily; over 6 years, 50-100 mg. daily; in divided doses. For adults: 25 mg. t.i.d. to 100 mg. q.i.d. *Supplied:* Tablets 10 mg. and 25 mg., in bottles of 100 and 500. Tablets 100 mg., in bottles of 100. Syrup, 2 mg. per cc., in pint bottles. Also available: Parenteral Solution. Prescription only.

References: 1. Freedman, A. M.: Pediat. Clin. North America *5*:573 (Aug.) 1958. 2. Nathan, L. A., and Andelman, M. B.: Illinois M. J. *113*:171 (Oct.) 1957. 3. Santos, I. M. H., and Unger, L.: Ann. Allergy *18*:179 (Feb.) 1960. 4. Litchfield, H. R.: New York J. Med. *60*:518 (Feb. 15) 1960.

ATARAX®

(brand of hydroxyzine)

PASSPORT TO TRANQUILITY

Pfizer

New York 17, N. Y.
Division, Chas. Pfizer & Co., Inc.
Science for the World's Well-Being®

VITERRA® Capsules—Tastitabs®
—Therapeutic Capsules for
vitamin-mineral supplementation

RESTORE VITALITY... to "the under-par child"*

NEW Zentron™

comprehensive liquid hematinic

- corrects iron deficiency
- restores healthy appetite
- helps promote normal growth

* underweight, easily fatigued, anorexic—due to mild anemia

Each 5-cc. teaspoonful provides:

Ferrous Sulfate (equivalent to 20 mg. of iron)	100	mg.
Thiamine Hydrochloride (Vitamin B_1)	1	mg.
Riboflavin (Vitamin B_2)	1	mg.
Pyridoxine Hydrochloride (Vitamin B_6)	0.5	mg.
Vitamin B_{12} Crystalline	5	mcg.
Pantothenic Acid (as *d*-Panthenol)	1	mg.
Nicotinamide	5	mg.
Ascorbic Acid (Vitamin C)	35	mg.

Alcohol, 2 percent.

Usual dosage:

Infants and children—1/2 to 1 teaspoonful (preferably at mealtime) one to three times daily.

Adults—1 to 2 teaspoonfuls (preferably at mealtime) three times daily.

Zentron™ (iron, vitamin B complex, and vitamin C, Lilly)

116801

Lilly
QUALITY / RESEARCH / PRODUCTS

"*Infants took the suspension without any untoward reactions.*"[1]

1. Reichelderfer, T.E., et al.: Antibiotics Annual, p. 899, 1959-1960.

why you can expect more from . . .

ILOSONE®

Ilosone, in its more acid-stable form, eliminates the need for an "empty stomach" for effective antibiotic therapy. Food no longer interferes with absorption to any great extent. Moreover, enhanced absorption from the intestine in comparison with that of older forms of erythromycin assures greater certainty of therapeutic response. Thirdly, Ilosone is notably well tolerated. In a review of over 20,000 case reports, there were no serious side-effects or toxic reactions.

Summing up: Ilosone works decisively in a wide variety of infections.

Usual dosage: For infants and for children under twenty-five pounds of body weight, 5 mg. per pound every six hours; for children weighing twenty-five to fifty pounds, 125 mg. every six hours.

For adults and for children over fifty pounds, 250 mg. every six hours.

In more severe or deep-seated infections, these dosages may be doubled.

Available in Pulvules®, suspension, and drops.

Ilosone® (propionyl erythromycin ester lauryl sulfate, Lilly)

119901

a breathing spell from asthma

Quadrinal*

a rapid way to clear the airway

- **stops wheezing**
- **increases cough effectiveness**
- **relieves spasm**

two dosage forms for convenient pediatric use

New Quadrinal Suspension — Pleasant fruit flavor is liked by children of all age groups. Readily compatible with milk, fruit juice or other fluids. Each teaspoonful of QUADRINAL SUSPENSION equals ½ QUADRINAL TABLET.

Quadrinal Tablets "... the tablet is easily broken into ½ or ¼ tablet for use in children and even infants. The rapid effect of ephedrine and theophylline is combined with the slower action of potassium iodide for more complete relief in asthma, bronchitis and emphysema." Seltzer, A., M. Ann. Dist. of Columbia, 26:17 (Jan.) 1957.

Each QUADRINAL TABLET contains ephedrine HCl (24 mg.), phenobarbital (24 mg.), 'Phyllicin'* (theophylline-calcium salicylate) (130 mg.), and potassium iodide (0.3 Gm.).

Indications: Quadrinal is indicated in bronchial asthma, chronic bronchitis, pulmonary fibrosis, and pulmonary emphysema.
Note: Caution is indicated with patients sensitive to iodides, in hyperthyroidism and cardiovascular disease.

Dosage: QUADRINAL TABLETS — the average adult dose is 1 tablet every three or four hours during the day, and if needed, 1 tablet upon retiring. For children 6 to 12 years of age, ½ tablet three times daily.

QUADRINAL SUSPENSION — the average dose for adults and children over 12 years of age is 2 teaspoonfuls three times daily; for children 6 to 12 years of age, 1 teaspoonful three times daily; for children under 6, adjust dose to body weight.

KNOLL PHARMACEUTICAL COMPANY, ORANGE, NEW JERSEY

*Quadrinal, Phyllicin®

IN STRESS SITUATIONS

• hot weather • fever • illness

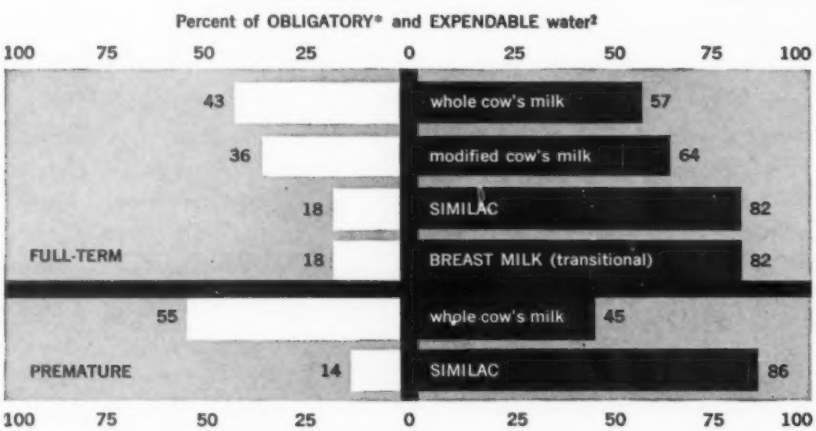
physiologic protection for infants—with SIMILAC®

"The osmolar load is an important factor in infant feeding since the kidneys can excrete a urine of only a limited osmolar concentration. . . . In addition to producing good nutrition under conditions with low extrarenal losses of water, **milk mixtures must be appropriate for infants requiring high extrarenal losses of water.**"[1]

In young infants under normal conditions, **the average renal solute concentration from whole cow milk formulas may be more than twice the concentration from Similac, a low osmolar feeding.**[2] But in the presence of high environmental temperatures and in conditions causing heat stress and body water loss, the urinary osmolar concentration may be expected to reach a maximum. The consequent decrease in expendable water for renal excretion may then cause undue demands to be made on body water for the renal excretion of the end products of whole cow milk formulas.[1,3]

The results of a recent study[2]: with 42 full term and 7 premature infants

"There was a larger amount of unobligated or expendable renal water in the infants fed the [Similac] than in those fed whole cow's milk . . . the margin of safety with [a whole cow milk formula] with regard to water requirements would be greatly reduced when extrarenal water losses are excessive."[2]



*"Among young infants there is a variability in the capacity of the kidney to excrete a solute load at a given rate and concentration. . . . [Although] it is known . . . that some full-term newborn infants and older premature infants may concentrate to much higher levels . . . , for the purposes of this study, it is assumed to be 700 mOsm per liter."[2]

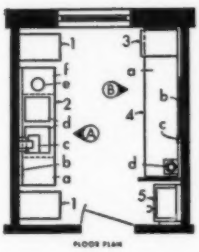
PERCENTAGES OF OBLIGATORY AND EXPENDABLE RENAL WATER DEMONSTRATE STILL FURTHER THE PHYSIOLOGIC SIMILARITY BETWEEN BREAST MILK AND SIMILAC: there is no closer nutritional equivalent to the milk of healthy, well-nourished mothers.

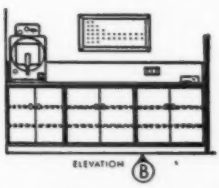
References: 1. Darrow, D. C., et al.: Pediatrics 14:602 (Dec.) 1954. 2. Calcagno, P. L., and Rubin, M. I.: J. Pediat. 56:717 (June) 1960. 3. Committee on Nutrition, American Academy of Pediatrics: Pediatrics 19:339 (Feb.) 1957.

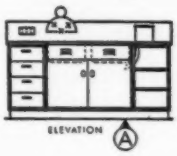
ROSS LABORATORIES Columbus 16, Ohio

HERE!-------

a low cost practical technic for the small INFANT-FORMULA ROOM







The Amsco electric heat Model 832 Formula Sterilizer enables hospitals with one to eight bassinets to carry out advanced techniques formerly possible only with large capacity equipment costing much more. Its capacity of 32 four or eight ounce bottles is ample to serve eight bassinets, using two cycles per day. The Model 832 requires minimum attention from the operator because complete cycling is automatic and forgetproof according to the time, temperature and exhaust settings selected.

Permits a Modern Formula Room in the minimum area.

With the model 832 as the basic unit, Amsco has developed special techniques and complete equipment suitable to Formula Room planning for the small nursery. Layout and equipment are fully in harmony with the most advanced standards of infant formula processing and work simplification . . . yet the space requirements and all-inclusive cost are extremely modest.

For complete information on the small Infant Formula Room, write for bulletin SC-319. (Hospitals with larger nurseries should request brochure SC-320R.)

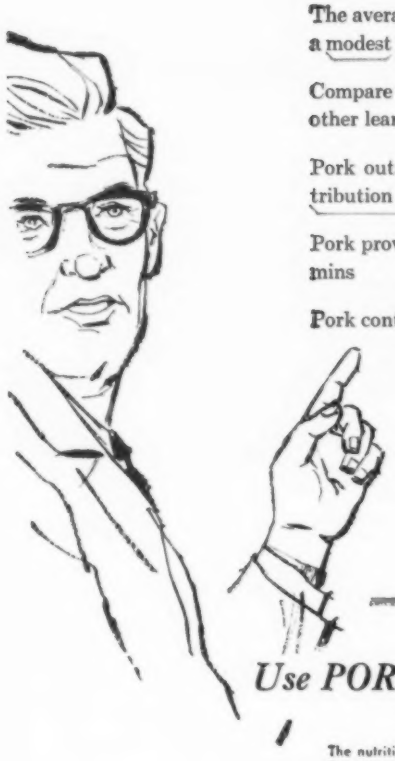
World's largest Designer and Manufacturer of Surgical Sterilizers, Tables, Lights and related equipment.

AMERICAN STERILIZER

ERIE • PENNSYLVANIA

pork in its proper place...

in the daily diet



The average serving of 100 gm. of lean pork provides a modest 250 calories.(1)

Compare the fat content of lean pork with that of other lean meats.

Pork outranks other high-protein foods in its contribution of thiamine.(B1)

Pork provides an important amount of other B vitamins

Pork contributes significant amounts of the essential minerals, iron, copper and phosphorus, magnesium and potassium, supplied in a form that the body can use readily.

1. Leverton, R.M., and Odell, G.V.: The Nutritive Value of Cooked Meat, Oklahoma Agricultural Experiment Station, Oklahoma State University, Miscellaneous Publication MP-49, 1958.

Use PORK—to tempt jaded appetites

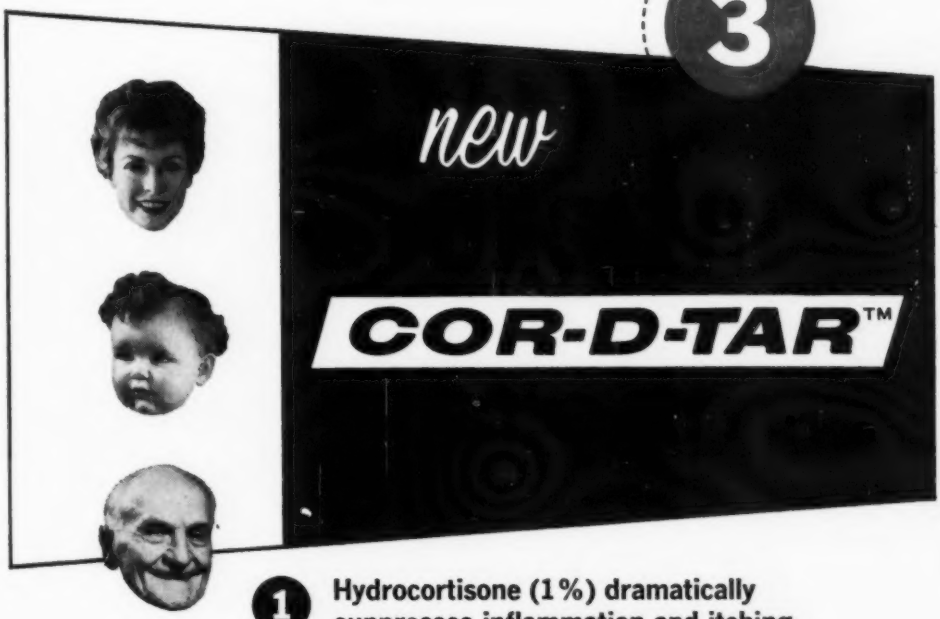
The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

AMERICAN MEAT INSTITUTE

MAIN OFFICE, CHICAGO • MEMBERS THROUGHOUT THE NATION

even seemingly "intractable" dermatoses

often yield 1 2 3



1 Hydrocortisone (1%) dramatically suppresses inflammation and itching.

2 Diiodohydroxyquin (2%) combats bacterial and fungal infection.

3 A superior coal tar solution (3%) specific aid in correction of eczematous manifestations.

In a stainless, water-miscible, cosmetically elegant cream base.

This combination of three unsurpassed topical agents rapidly controls even resistant subacute and chronic dermatoses, especially when inflammation occurs with itching, scaling and secondary infection... **in eczemas (infantile and adult), atopic dermatitis, pyodermas, etc.**

Patients will appreciate the rapidity with which **DESITIN COR-D-TAR CREAM** *controls distress and promotes the healing process.* Tubes of ½ and 1 ounce.

DESITIN CHEMICAL COMPANY
812 Branch Avenue, Providence 4, R. I.

STOPS THE ASTHMA ATTACK
IN MINUTES...FOR HOURS...
ORALLY

ELIXOPHYLLIN®

RAPID RELIEF IN MINUTES—in 15 minutes[1,2,3] mean theophylline blood levels are comparable to I. V. aminophylline—so that severe attacks have been terminated in 10 to 30 minutes.[1,4,5,6]

SUSTAINED RELIEF FOR HOURS—After absorption theophylline is slowly eliminated during a 9-hour period,[7] making possible t.i.d. 'round-the-clock protection in chronic cases. **Note:** *With Elixophyllin the patient can learn to abort an attack in its incipient stage.*

NO UNNEEDED SIDE EFFECTS—Since Elixophyllin does not need "auxiliaries," it contains no ephedrine—no barbiturate—no iodide—no steroid. *Gastric distress is rarely encountered.*[8,9]

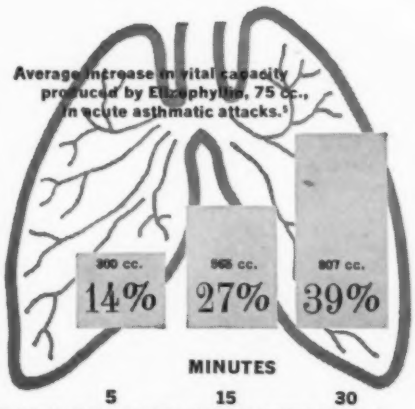
Each tablespoonful (15 cc.) contains theophylline 80 mg. (equivalent to 100 mg. aminophylline) in a hydro-alcoholic vehicle (alcohol 20%).

ACUTE ATTACKS:

single dose of 75 cc. for adults; 0.5 cc. per lb. of body weight for children.

24 HOUR CONTROL:

for adults 45 cc. doses before breakfast, at 3 P.M., and before retiring; after two days, 30 cc. doses. Children, first 6 doses 0.3 cc.—then 0.2 cc. per lb. of body weight as above.



REFERENCES: 1. Kessler, F.: Connecticut M.J. *21*:205 (March) 1957. 2. Schluger, J.; McGinn, J.T., and Hennessy, D.J.: Am. J. Med. Sci. *233*:296 (March) 1957. 3. Kessler, F.: Med. Times (Oct.) 1959. 4. Burbank, B.; Schluger, J., and McGinn, J.: Am. J. Med. Sci. *234*:28 (July) 1957. 5. Spielman, A.D.: Ann. Allergy *15*:270 (June) 1957. 6. Greenbaum, J.: Ann. Allergy (May-June) 1958. 7. Waxler, S.H., and Shack, J.A.: J.A.M.A. *143*:736 (1950). 8. Bickerman, H.A., and Barach, A.L., in Modell, W.: Drugs of Choice 1960-1961, St. Louis, The C.V. Mosby Company, 1960, p. 516. 9. Wilhelm, R.E., Conn, H.F.: in Current Therapy—1961, Philadelphia, W.B. Saunders Company, p. 417.

Patent Pending

Reprints on request

Sherman Laboratories
Detroit 11, Michigan

color, aroma, taste.....all orange!!

PALADAC®

Liquid Vitamin Preparation

The three oranges of PALADAC make it a triple favorite with children because they love its lively orange color...its fragrant orange aroma...and its delicious orange flavor. A well-balanced nine vitamin formula, PALADAC is valuable for prevention of vitamin deficiencies. It may be given directly or incorporated into milk, fruit juice, or practically any other food. And PALADAC is stable...requires no refrigeration. *available:* 4-ounce and 16-ounce bottles.

03661

PARKE-DAVIS

PARKE, DAVIS & COMPANY, Detroit 32, Michigan

The discomfort following my tonsillectomy was almost nonexistent. I could eat and swallow without feeling pain because my doctor gave me Xylocaine... whatever that is!

Xylocaine® Viscous topical anesthetic for oral administration
(brand of lidocaine*)

For almost immediate relief of pain and easier swallowing after T & A, Xylocaine Viscous spreads evenly and adheres to the membranes. Cherry flavored Xylocaine Viscous contains 2% Xylocaine hydrochloride; water miscible and of viscous consistency. Dose: 1 teaspoonful, swished around in the mouth, and then swallowed slowly. Astra Pharmaceutical Products, Inc., Worcester 6, Mass.

ASTRA

*U.S. Patent No. 2,441,498

for
Prickly Heat

—"a minor disorder of major proportions."[1]

COOL

AVEENO®
COLLOID BATHS

Since heat and sweating intensify prickly heat,[1] removal to a cool environment and reduction of sweating is an important first step in relieving the patient.

Waisman[2] suggests colloidal baths, using "1 cupful of . . . Aveeno to the tub of cool water" for relief.

This simple technique affords immediate temperature reduction and alleviation of sweating . . . as well as relief from itching by virtue of *colloidal oatmeal*, used for over a decade as an excellent antipruritic and anti-inflammatory agent.

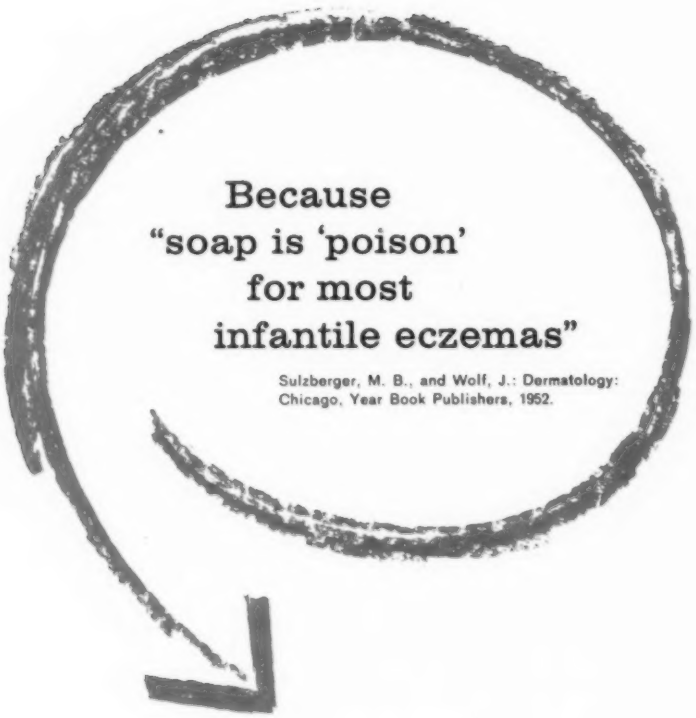
AVEENO COLLOIDAL OATMEAL
is available in 18 oz. and 4 lb. boxes.

ALSO EXCELLENT FOR POISON IVY AND POISON OAK

References: 1. Pillsbury, D. M., Shelley, W. B., and Kligman, A. M.: Dermatology. Philadelphia, W. B. Saunders Company, 1956. 2. Waisman, M.: in Current Therapy, 1960. Ed. by Conn; Phila., W. B. Saunders Co.

Also available: AVEENO® OILATED (soothing colloidal oatmeal *plus* 35% emollient oils) for dry dermatoses.

AVEENO CORPORATION
250 West 57th Street, New York 19, N. Y.
Pioneers in Ethically Promoted Colloid Baths



AVEENO®-BAR

for soap-free cleansing

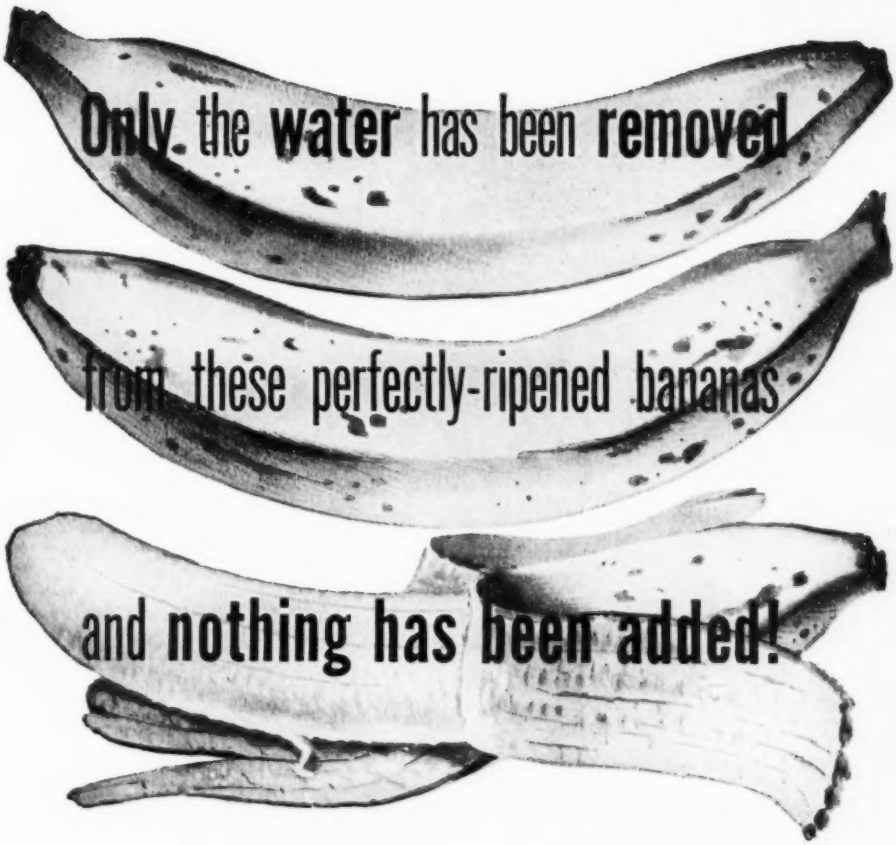
Aveeno-Bar is a richly-lathering soap-free cleansing bar that contains more than 50% soothing colloidal oatmeal. It is particularly well-suited to cleansing sensitive atopic skin.

It contains no soap whatsoever, and, unlike soap, contains no fatty acids which may aggravate an already irritated condition. Aveeno-Bar has a pH of 5.7 to approximate the normal pH of skin. It lathers richly even in the hardest water.

Active Ingredients: Aveeno Colloidal Oatmeal; special blend of sudsing agents; dewaxed hypo-allergenic lanolin; hexachlorophene.

AVEENO CORPORATION 250 WEST 57TH STREET NEW YORK 19, N. Y.

CO AB 54



Kanana Banana Flakes for *instant* mashed banana in daily routine feeding!

• PURE • PERFECTLY RIPE
• FULLY NUTRITIOUS

The addition of three parts water or milk will INSTANTLY provide the wholly-nutritious mashed banana you prescribe.

When you prescribe banana, write "Kanana"!

Kanana Banana Flakes (NOT A POWDER)

FREE SAMPLE! Fill out and mail TODAY! For content analysis and free sample, send to:
Kannengiesser & Co., 76 Ninth Ave., New York 11, N. Y.

NAME

STREET

CITY ZONE STATE

KANNENGIESSER & COMPANY, 76 NINTH AVE., NEW YORK 11, NEW YORK. In Canada: Laurentian Agencies, Ltd., 429 St. Jean Baptiste Street, Montreal, Canada

Allergic or inflammatory flare-up!

Female. 41. Dx: dermatitis venenata. Contactant: calamine-antihistamine lotion applied for contact dermatitis—Rx Celestone Tablets, 0.6 mg. Photograph prior to Rx.

Step-down dosage of 1 tab. q.i.d. for 2 days, 1 tab. t.i.d. for 2 days, 1 tab. b.i.d. for 2 days and 1 tab. daily for 8 days. Results: condition completely cleared. Side Effects: none. Photograph after 72 hours of Celestone therapy. (Photographs courtesy of M. M. Nierman, M.D., Calumet City, Ill.)

Schering

Rapid remission with new Celestone

the first major advance in corticosteroid therapy in over 2½ years

Clinical worth: CELESTONE provides greatly enhanced antiallergic and anti-inflammatory effects with significantly lower mg. dosages. Its efficacy and safety have been established by 20 months of pre-introductory clinical trials in such steroid-responsive disorders as:

- bronchial asthma
- pollenosis (severe hay fever)
- allergic/inflammatory dermatoses
- inflammatory eye diseases
- rheumatoid arthritis

Exceptional utility: From simple dermatoses to the more severe steroid-responsive conditions, the unexcelled anti-inflammatory effect of CELESTONE provides rapid clinical improvement with average daily dosages of from 2 to 8 tablets.

Ease of use: CELESTONE has simple-to-follow dosage schedules for all steroid-responsive disorders based on a single tablet strength, 0.6 mg. Patients may be switched easily from other corticosteroids to CELESTONE with proper dosage adjustments.

Safety-speed factor: CELESTONE is particularly valuable for short-term therapy of acute inflammatory episodes because inflammation is resolved quickly, thus helping to avoid certain corticoid side effects such as:

- weight loss
- anorexia
- vertigo
- severe headache
- sodium and water retention
- muscle weakness
- potassium excretion

Improved response: CELESTONE also offers the advantage of providing an opportunity to restore "lost" or diminished control in patients receiving other steroids.

For complete details, consult latest Schering literature available from your Schering Representative or the Medical Services Department, Schering Corporation, Bloomfield, New Jersey.

Bibliography: 1. Goldman, L.: Investigation of a New Steroid in Dermatology. Paper presented at First Symposium on the Clinical Application of Betamethasone: A New Corticosteroid, New York City, May 8, 1961. 2. Nierman, M. M.: The Use of Betamethasone in Dermatology. *Ibid.* 3. Gant, J. Q., and Gould, A. H.: Betamethasone: A Clinical Study. *Ibid.* 4. Frank, L.: The Place of Betamethasone in Dermatologic Practice. *Ibid.* 5. Hampton, S. F.: Betamethasone—A New Steroid in Allergy: A Preliminary Report. *Ibid.* 6. Bukantz, S. C.: Observations on the Use of Betamethasone in the Intractable Asthmatic Child. *Ibid.* 7. Bedell, H.: A New Systemic Steroid in the Treatment of Allergies in Office Practice. *Ibid.* 8. Schwartz, E.: Clinical Evaluation of Betamethasone in Chronic Intractable Bronchial Asthma. *Ibid.* 9. Kammerer, W. H.: Observations on the Effects of Betamethasone in Rheumatoid Arthritis. *Ibid.* 10. Cohen, A., and Goldman, J.: Management of Rheumatoid Arthritis with a New Steroid. *Ibid.* 11. Gordon, D. M.: Betamethasone—A New Corticosteroid in Ophthalmology. *Ibid.* 12. Abrahamson, I. A., Jr.: A Clinical Evaluation of Betamethasone. *Ibid.*

H-371

(betamethasone) **Tablets, 0.6 mg.**

CELESTONE™

a new magnitude in corticosteroid activity

from the

mother's point of view

S-M-A assures balanced nutrition

. . . keeps her baby healthy and thriving

Setting the Standard in Infant Formulas

S-M-A®

Food Formula for Infants

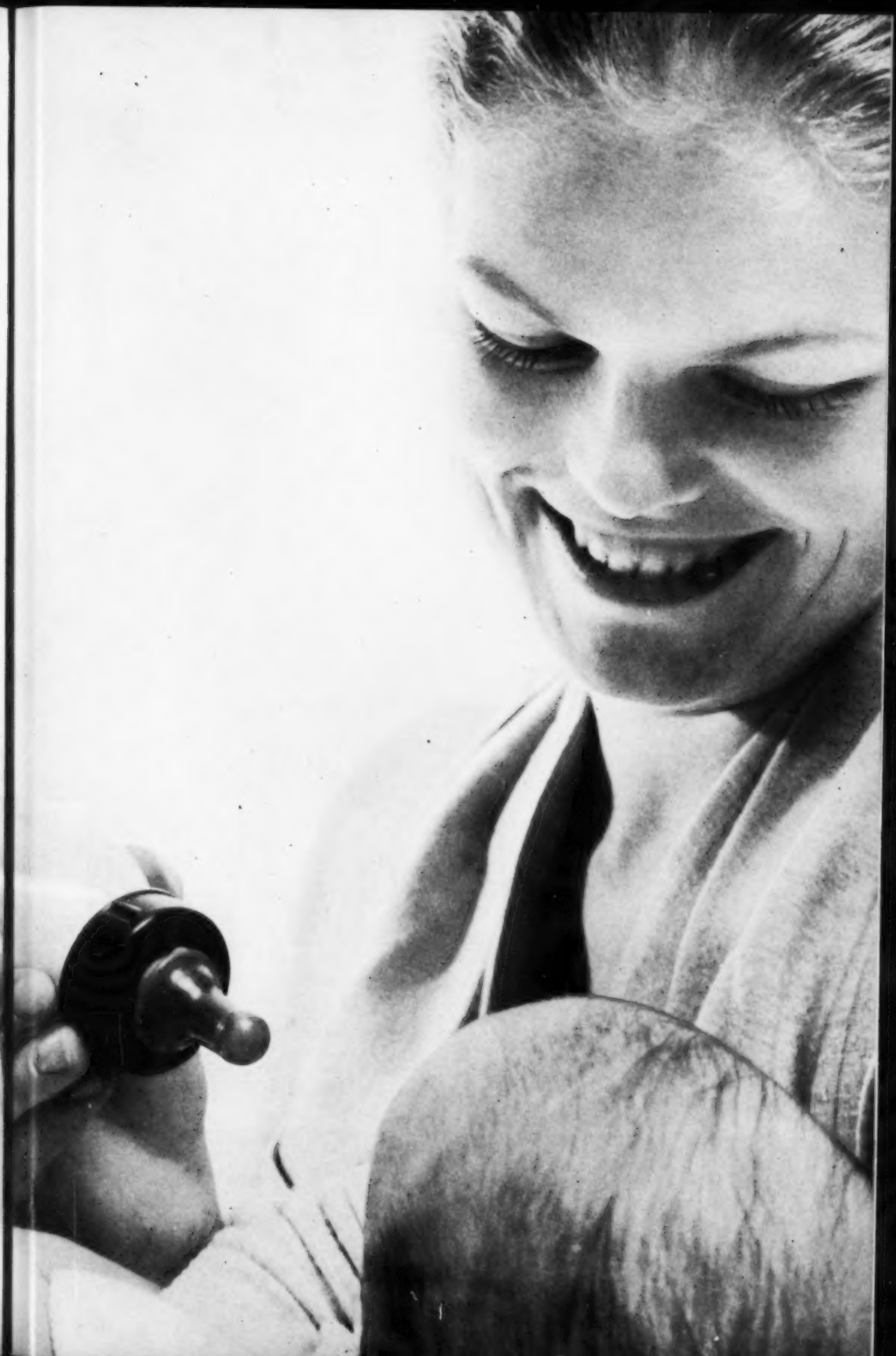
Wyeth®

S-M-A—the first formula successfully patterned after breast milk—provides a balanced diet of all known essential nutrients to promote health and growth. No need for supplementation.

convenient . . . time-saving . . . economical
Complete in all known essentials, S-M-A requires only the addition of water. There's no problem of changing measurements, no risk of mothers forgetting supplementation. S-M-A fully satisfies hunger and infant nutrition requirements. It's convenient . . . easy-to-prepare . . . and economical of time and money.

Wyeth Laboratories Philadelphia 1, Pa.

Wyeth
SERVICE TO MEDICINE



no longer
detoured
by
diarrhea

DONNAGEL®

Donnatal® with Kaolin and Pectin compound

Robins

DONNAGEL's comprehensive antidiarrheal formulation gives the green light to normal activity, through its fast and dependable control of intestinal hypermotility.

Each 30 cc. (1 fl. oz.) of DONNAGEL contains:

Kaolin	6.0 Gm.	Natural belladonna alkaloids:	
Pectin	142.8 mg.	hyoscyamine sulfate	0.1037 mg.
Phenobarbital (1/4 gr.)	16.2 mg.	atropine sulfate	0.0194 mg.
		hyoscine hydrobromide	0.0065 mg.

also available

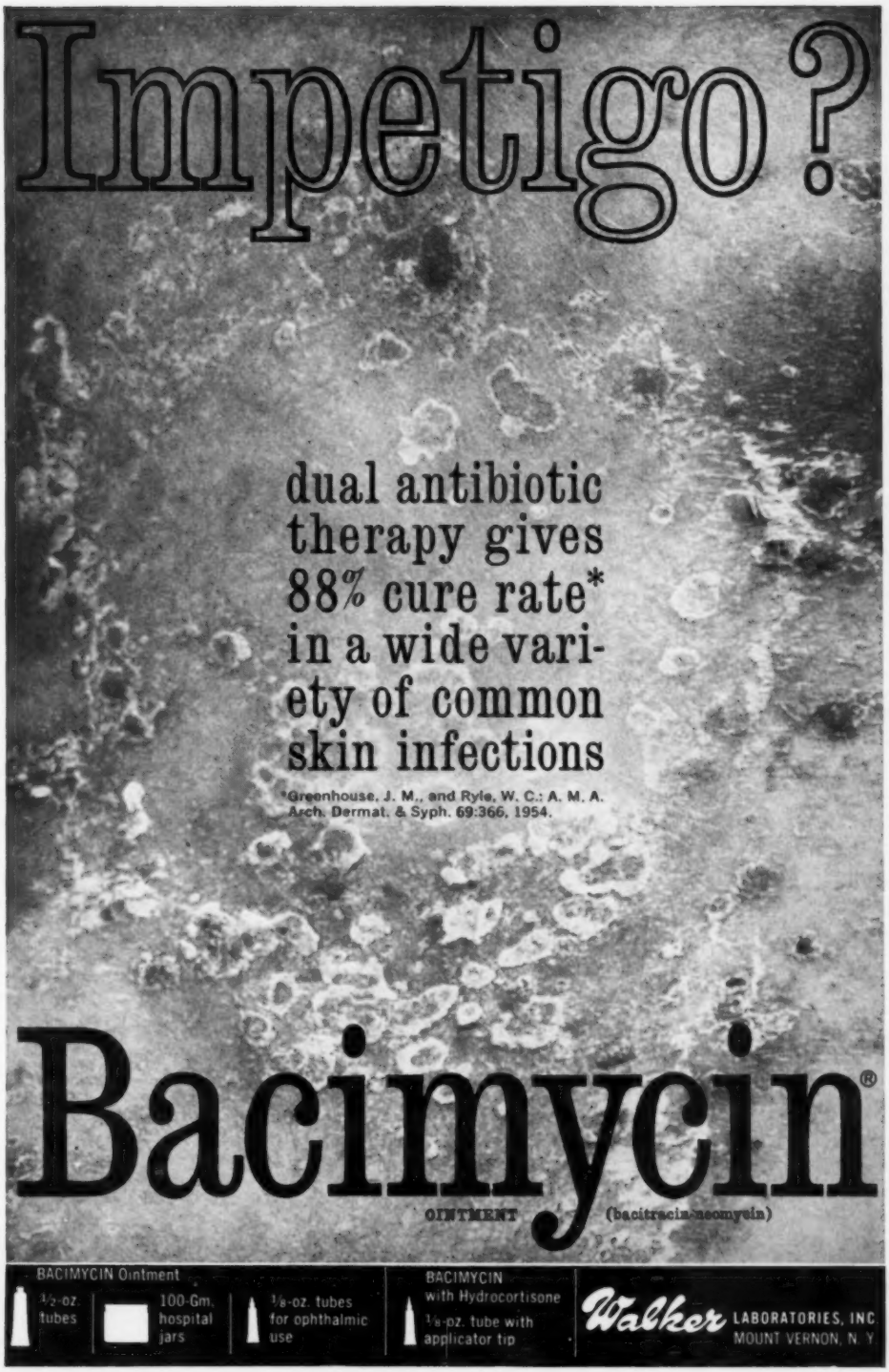
DONNAGEL® WITH NEOMYCIN • DONNAGEL®-PG

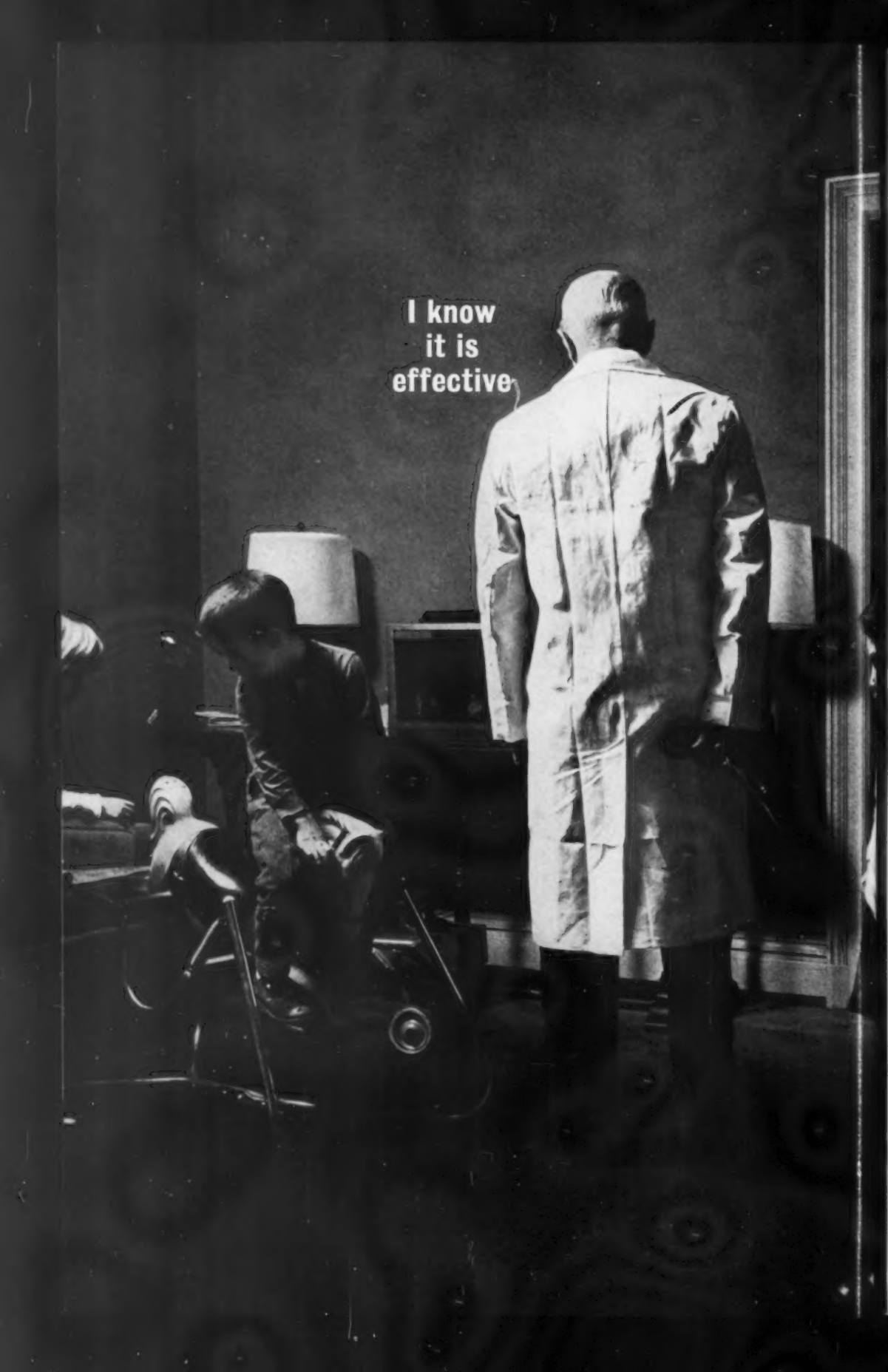
DONNAGEL plus neomycin sulfate 300 mg. (as neomycin base 210 mg.) per 30 cc.

DONNAGEL plus powdered opium U.S.P. 24.0 mg. per fl. oz. (equivalent to paregoric 6 ml.). This is the usual adult dose.

All three forms available in bottles of 6 fl. oz.

A. H. ROBINS COMPANY, INC., RICHMOND 20, VIRGINIA


Impetigo?
dual antibiotic therapy gives 88% cure rate* in a wide variety of common skin infections
*Greenhouse, J. M., and Ryle, W. C.: A. M. A. Arch. Dermat. & Syph. 69:366, 1954.
Bacimycin®
OINTMENT (bacitracin-neomycin)
BACIMYCIN Ointment
½-oz. tubes
100-Gm. hospital jars
⅛-oz. tubes for ophthalmic use
BACIMYCIN with Hydrocortisone
⅛-oz. tube with applicator tip
Walker LABORATORIES, INC.
MOUNT VERNON, N. Y.



The co
apy in
the ra
in bod
concen
charac
tant i
10-yea
palata
flavor

Science

dependable blend of effectiveness, toleration, and acceptability for pediatric antibiotic therapy

Cosa-Terrabon®

OXYTETRACYCLINE WITH GLUCOSAMINE

ORAL SUSPENSION / PEDIATRIC DROPS

today's pediatric *forms of Terramycin*

The continuing effectiveness of Terramycin therapy in pediatric infections derives as always from the rapid absorption; notably wide distribution in body tissues and fluids; high, active urinary concentrations; and broad anti-infective spectrum characteristic of oxytetracycline. Equally important in pediatrics, Terramycin therapy offers a 10-year record of exceptional toleration plus easy, palatable administration in deliciously fruit-flavored, preconstituted liquid form.

IN BRIEF

Cosa-Terrabon provides oxytetracycline (Terramycin®) with glucosamine for maximum absorption. Because Cosa-Terrabon is preconstituted, stable, and unusually well accepted by children, waste of medication is largely avoided.

INDICATIONS: Because oxytetracycline is effective against both gram-positive and gram-negative bacteria, rickettsiae, spirochetes, large viruses, and certain parasites (e.g., amebae, pinworms), Cosa-Terrabon is indicated in a great variety of pediatric infections due to susceptible organisms, e.g., infections of the respiratory, gastrointestinal and genitourinary tracts, surgical and soft-tissue infections, ophthalmic and otic infections, and many others.

ADMINISTRATION AND DOSAGE: For infants and children, 10 to 20 mg. of Terramycin per pound of body weight daily, in divided doses, is usually effective.

SIDE EFFECTS AND PRECAUTIONS: Antibiotics may allow overgrowth of non-susceptible organisms—particularly monilia and resistant staphylococci. If this occurs, discontinue medication and institute indicated supportive therapy and treatment with other appropriate antibiotics. Aluminum hydroxide gel has been shown to decrease antibiotic absorption and is therefore contraindicated. Glossitis and allergic reactions are rare. There are no known contraindications to glucosamine.

SUPPLIED: *Cosa-Terrabon Oral Suspension*—125 mg. per 5 cc. teaspoonful, bottles of 2 oz. and 1 pint; and *Cosa-Terrabon Pediatric Drops*—5 mg. per drop (100 mg. per cc.), 10 cc. bottle with calibrated plastic dropper. Terramycin is also available as *Cosa-Terramycin® Capsules*, 250 mg. and 125 mg.; and as *Terramycin Intramuscular Solution, conveniently preconstituted*, in the new 10 cc. multi-dose vial, 50 mg. per cc., and in 2 cc. prescored glass ampules, containing 100 mg. or 250 mg., packages of 5 and 100. In addition, a variety of other systemic and local dosage forms are available to meet specific therapeutic requirements.

More detailed professional information available on request.

Science for the world's well-being® Pfizer PFIZER LABORATORIES *Division, Chas. Pfizer & Co., Inc. Brooklyn 6, New York*

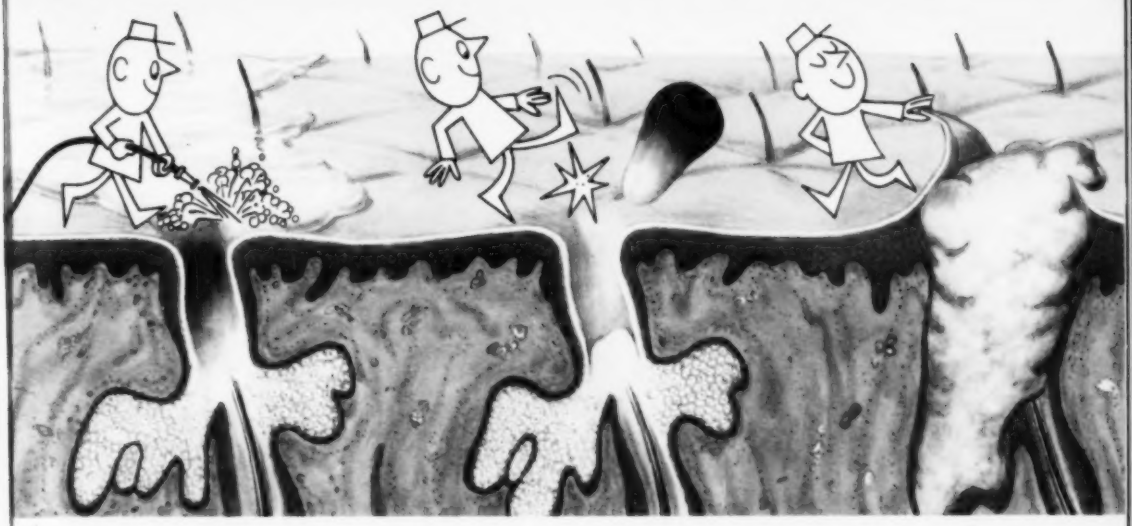
because it's so easy to give...and so easy on the patient

Children offer little or no resistance to this enema unit specifically designed for pediatric use. The compact FLEET ENEMA PEDIATRIC avoids the discomfort of large volumes of liquid...takes only a minute. Insertion is made easier and safer because of the pre-lubricated, anatomically correct 2-inch rectal tube.[1] FLEET ENEMA PEDIATRIC can be prescribed with confidence as "a safe and effective enema preparation for even small children."[2]

FLEET ENEMA *Pediatric*, 2¼ fl.oz. *Regular* FLEET ENEMA, 4½ fl.oz. *Each 100 cc. contains* 16 Gm. sodium biphosphate and 6 Gm. sodium phosphate. *Also available:* FLEET® OIL RETENTION ENEMA, 4¼-fl.oz. ready-to-use unit containing Mineral Oil U.S.P.

1. Frech, H. C., and Lanier, L. R., Jr.: Am. J. Obst. & Gynec. 74:1146, 1957. 2. Way, W. G., et al.: Virginia M. Month. 85:291. 1958.

C. B. FLEET CO., INC. LYNCHBURG, VIRGINIA



Fostex® treats pimples·blackheads·acne while they wash

degreases the skin
· helps remove blackheads
dries and peels the skin

Patients like Fostex because it's so easy to use. Instead of using soap, they simply wash acne skin with Fostex Cream or Fostex Cake 2 to 4 times daily.

Fostex contains: Sebulytic® base (unique, penetrating, surface-active combination of soapless cleansers and wetting agents*) with remarkable antiseborrheic, keratolytic and antibacterial actions . . . enhanced by micropulverized sulfur 2%, salicylic acid 2% and hexachlorophene 1%.

*sodium lauryl sulfoacetate, sodium alkyl aryl polyether sulfonate and sodium dioctyl sulfosuccinate.

Fostex Cream and Fostex Cake are interchangeable for therapeutic washing of the skin. Fostex Cream is approximately twice as drying as Fostex Cake. Supplied: Fostex Cake—bar form. Fostex Cream—4.5 oz. jars. Also used as a therapeutic shampoo in dandruff and oily scalp.

And . . . since continuous 24-hour drying and peeling of acne skin is essential, FOSTRIL (a new, flesh-tinted drying lotion) should be used once or twice daily in addition to Fostex therapeutic washings. Fostril® contains Liposec®(polyoxyethylene lauryl ether), a new, surface-active drying agent used for the first time in acne treatment. This agent, with 2% micropulverized sulfur and a zinc oxide, talc and bentonite base, provides Fostril with excellent drying properties. Fostril also contains 1% hexachlorophene.

Available: Fostril, 1½ oz. tubes. Fostril-HC (¼% hydrocortisone) 25 gm. tubes.

WESTWOOD PHARMACEUTICALS • Buffalo 13, New York

"We have observed that the routine use of the soapless lauryl sulfoacetate bar, (Lowila Cake) in all babies, decreases the incidence of soap irritation and aids in the protection against pyogenic dermatoses. We have also observed that 'heat rash' or miliaria in children is benefited by avoidance of soap and use of the soapless bar.

"Infants with diaper rash or ammoniacal dermatitis are definitely irritated by the alkaline effects of soap. In these babies the use of this nonirritating soapless cleanser, (Lowila) plus the reduction of exposure to the alkaline excreta, leads to immediate improvement."*

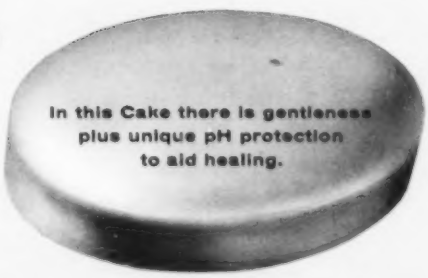
infantile eczema...diaper rash ...sensitive skin

When soap irritates or retards healing, change to

LOWILA® CAKE

Lowila Cake cleanses the skin gently, is completely soap-free and so mild its lather won't smart even a baby's eyes. Eighteen years' experience show Lowila to be virtually nonirritating and nonsensitizing. Even the delicate skin of the newborn infant, inclined to injury by ordinary soaps, is not harmed by sodium lauryl sulfoacetate (Lowila Cake).*

Lowila's unique pH protection creates an environment favorable to therapy and healing. Its acid pH is 4.5 to 5.5 (approximating that of normal skin). This is in contrast to high pH (7-11) of ordinary soaps.



Lowila Cake contains gentle-acting sodium lauryl sulfoacetate in a corn dextrin base acidified with lactic acid. Does not contain alkalis, fatty acids or perfumes. Lowila Cake has excellent cleansing properties and easily works into a rich, creamy lather. Supplied in bar form.
Write for samples. Also available in Canada.

*Nelson, L. S., and Stoesser, A. V.: Ann. Allergy *11*:572-579 (Sept.-Oct.) 1953.

WESTWOOD PHARMACEUTICALS
Buffalo 13, New York

How long can baby food be stored safely, after it's opened?

• **Perhaps you have been asked** this question by mothers of the babies in your care. Of course, there are variable factors which affect the keeping qualities of opened baby food, but as a general rule you may assure mothers:

Because of the careful sterilization which Heinz Baby Foods undergo, they can be stored safely in resealed jars for three days, provided the container is refrigerated between uses.

• **You can recommend** Heinz Baby Food with confidence. All are quality-controlled according to rigid laboratory standards in order to insure uniformity of nutritive value, flavor, color and consistency.

quality with economy

clinically proved oral penicillin therapy that costs your patients less

PENTIDS Squibb Penicillin G Potassium *Available in these convenient dosage forms:* Pentids '400' Tablets (400,000 u.) • Pentids '400' for Syrup (400,000 u. per 5 cc. when prepared) • Pentids Tablets (200,000 u.) • Pentids for Syrup (200,000 u. per 5 cc. when prepared) • Pentid-Sulfas Tablets (200,000 u. with 0.5 Gm. triple sulfas) • Pentid-Sulfas for Syrup (200,000 u. with 0.5 Gm. triple sulfas per 5 cc. when prepared) • Pentids Capsules (200,000 u.) • Pentids Soluble Tablets (200,000 u.)

For full information, see your Squibb Product Reference or Product Brief.

SQUIBB
Squibb Quality—the Priceless Ingredient

"PENTIDS" AND "PENTID-SULFAS" ARE SQUIBB TRADEMARKS.

Schering

HERE'S HOW DILODERM

HELPS YOUR PEDIATRIC SKIN PATIENTS—AND THEIR PARENTS IN ECZEMA, CONTACT DERMATITIS, NEURODERMATITIS

saves sleepless nights— promptly relieves itching, burning

saves time, accelerates healing
— buffered to approximate skin's acid mantle, helps restore normal skin pH

saves money — "measured-dose" valve prevents waste, overmedication

saves tears — Foam Aerosol simple and pleasant to apply

a variety of forms — Foam Aerosol, Aerosol, Cream — all forms also available with neomycin to combat infection

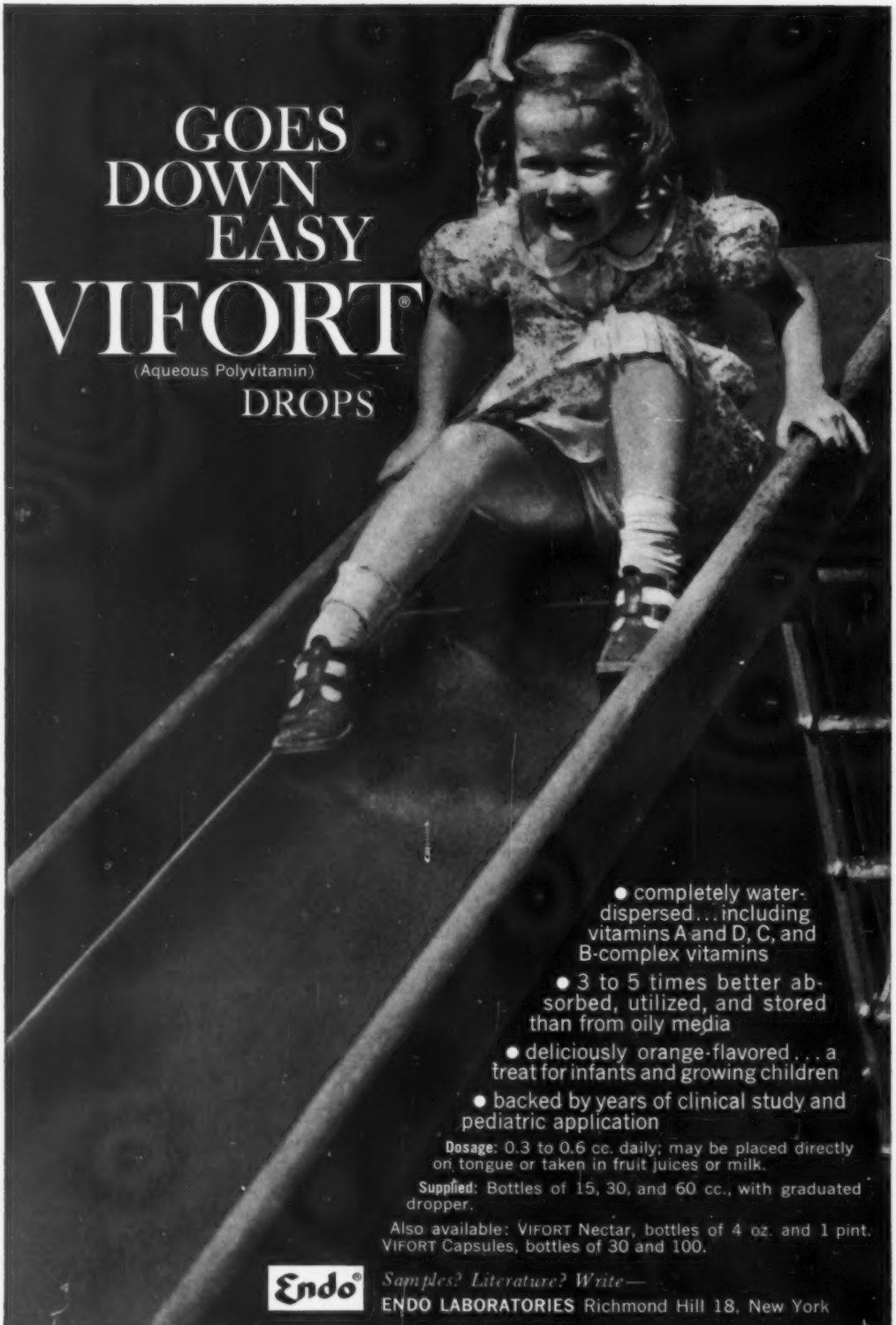
DILODERM™
dichlorisone acetate

Now available, NEW 15 Gm. economy-size tube of DILODERM or NEO-DILODERM Cream

Available with or without neomycin: Foam Aerosol, 10 Gm. dispenser, 18.75 mg. dichlorisone acetate or 18.75 mg. dichlorisone acetate with 37.5 mg. neomycin sulfate (equivalent to 26.25 mg. neomycin base); Aerosol, 50 Gm. container, 8.33 mg. dichlorisone acetate or 8.33 mg. dichlorisone acetate with 16.6 mg. neomycin sulfate; Cream, 5 Gm. tube, 2.5 mg./Gm. dichlorisone acetate or 2.5 mg./Gm. dichlorisone acetate with 5 mg./Gm. neomycin sulfate (equivalent to 3.5 mg./Gm. neomycin base).

For complete details, consult latest Schering literature available from your Schering Representative or Medical Services Department, Schering Corporation, Bloomfield, N.J.

S-755 JANUARY, 1961


GOES DOWN EASY
VIFORT®
(Aqueous Polyvitamin)
DROPS
• completely water-dispersed... including vitamins A and D, C, and B-complex vitamins
• 3 to 5 times better absorbed, utilized, and stored than from oily media
• deliciously orange-flavored . . . a treat for infants and growing children
• backed by years of clinical study and pediatric application
Dosage: 0.3 to 0.6 cc. daily; may be placed directly on tongue or taken in fruit juices or milk.
Supplied: Bottles of 15, 30, and 60 cc., with graduated dropper.
Also available: VIFORT Nectar, bottles of 4 oz. and 1 pint. VIFORT Capsules, bottles of 30 and 100.
Endo®
Samples? Literature? Write—
ENDO LABORATORIES Richmond Hill 18, New York

Each 0.6 cc. VIFORT Drops provides 5000 USP units vitamin A, 1000 USP units calciferol (D), 50 mg. ascorbic acid, 1.5 mg. thiamine (B_1), 1.2 mg. riboflavin (B_2), 10 mg. nicotinamide, 1 mg. pyridoxine (B_6) and 3 mg. d-panthenol, in a nonalcoholic base.

Otobiotic® Antibiotic/Antifungal EAR DROPS

Clinically Proven Results...controls infection/reduces exudation/stops pruritus/relieves pain/does not distort otic landmarks/physiologic pH/virtually nonsensitizing and nonirritating. FORMULA: Neomycin (from sulfate). 3.5 mg., and sodium propionate, 50 mg. per cc. Available in 15 cc. dropper bottles.

IN SWIMMER'S EAR!

Otobione® ANTI-INFLAMMATORY/Antibiotic/Antifungal EAR DROPS

Effective relief in 82% of 3334 cases.* Sterile Otic Drops—ideal for use when inflammation is present. Provides the same outstanding clinical benefits of Otobiotic, plus prednisolone for anti-inflammatory effectiveness. FORMULA: Prednisolone acetate, 5 mg., neomycin (from sulfate), 3.5 mg. and sodium propionate, 50 mg. per cc. Available in 5 cc. bottles with "steri-sealed" dropper.
*Case reports on file, White Laboratories.

PURE ANTIHISTAMINE ACTION

Dīsomer® SYRUP

(DEXBROMPHENIRAMINE MALEATE)

YOUR ALLERGIC PATIENT REMAINS ASYMPTOMATIC AND ALERT!

- highly effective
- side effects negligible
- delicious wild cherry flavor

SUPPLIED: 2 mg./tsp., pint bottles.
ALSO Chronotabs: (Sustained-Action Tablets) 4 mg. and 8 mg., bottles of 100.
Tablets: 2 mg., scored, bottles of 100.

Dīsophrol™

(FORMERLY DISOPHRIN)

In nasal congestion and rhinorrhea due to head colds, allergies and sinusitis—
Decongests Nasal and Sinus Passages...
Dries Mucous Secretions!

A sensibly simple formula: Disomer (dexbromphen-iramine maleate) 2 mg., d-isoephedrine sulfate 60 mg. Available in bottles of 100 scored tablets.

WHITE LABORATORIES, INC./ Kenilworth, New Jersey

ONLY

DESITIN®
Medicinal and Nursery
POWDER

is saturated with high grade Norwegian Cod Liver Oil (plus its vitamins A and D)... so will not "dry out" the skin, nor deprive it of its natural fats.

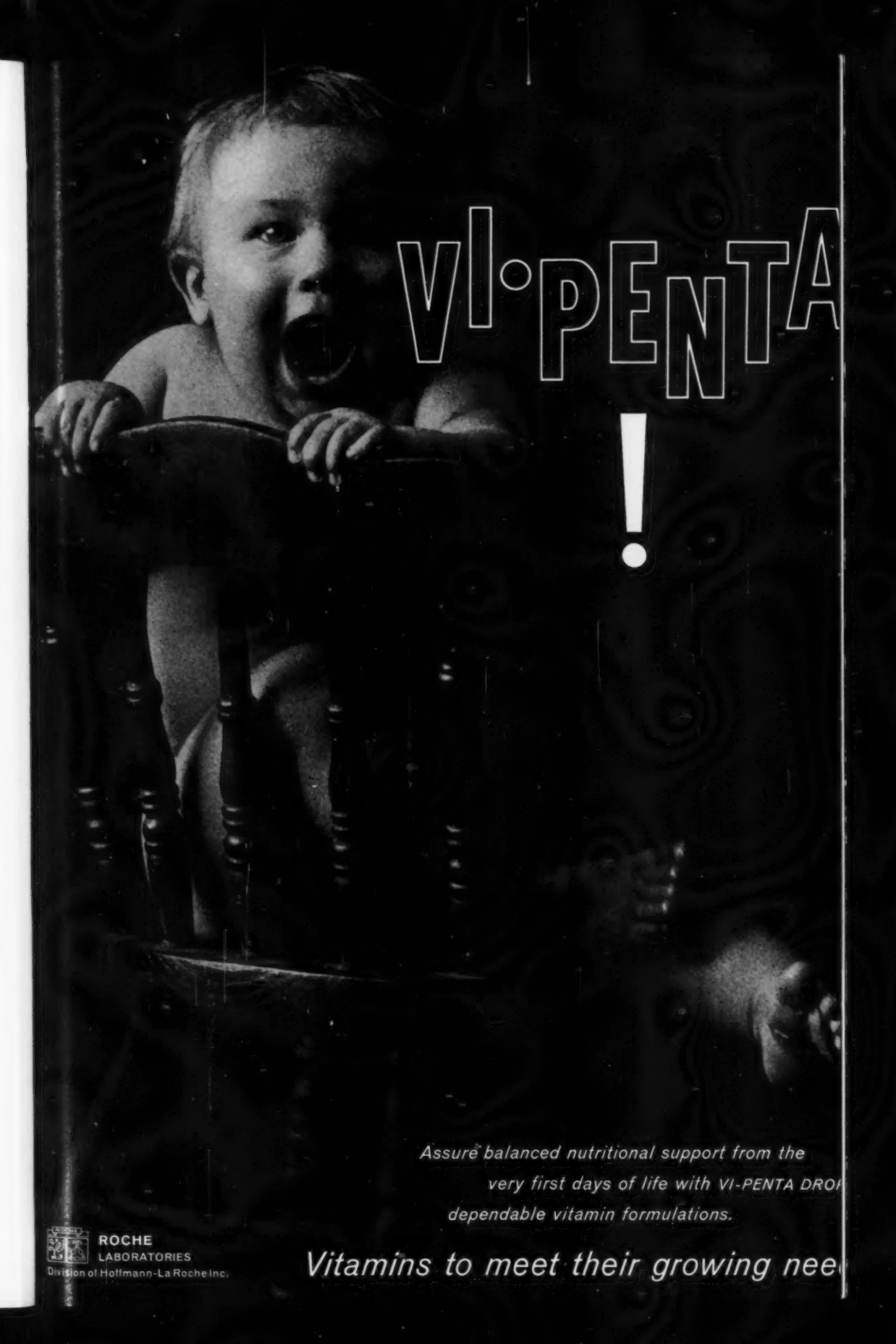
Instead... DESITIN POWDER acts to keep baby's skin normally lubricated, soft, smooth, **supple**..... in **diaper rash**
prickly heat rash
chafing, skin irritations

Every baby deserves the tender, loving care of soothing, protective, **healing** DESITIN POWDER.

Mothers will appreciate your recommendation of both DESITIN POWDER and DESITIN OINTMENT.

samples cheerfully sent—write **DESITIN CHEMICAL COMPANY**
812 Branch Ave., Providence 4, R. I.

DESITIN SOAP ... ideal for baby's bath!


VI·PENTA
!
Assure balanced nutritional support from the
very first days of life with VI-PENTA DROP
dependable vitamin formulations.
ROCHE
LABORATORIES
Division of Hoffmann-La Roche Inc.
Vitamins to meet their growing nee

Generation after Generation

DEVOTION

The devotion of a mother to her child is the very essence of true love. It begins at birth and endures all through life. This devotion is expressed by the tender loving care and protective vigilance she bestows upon her baby. As a further expression of devotion to her child, she seeks her physician's guidance and follows his advice.

The physician's devotion to a child is manifested in the measures he takes to safeguard the child's health. He gives particular attention to the child's nutritional needs right from birth because he knows that good nutrition is essential for the infant's normal growth, and future well-being. He recognizes the need for reliable formula products because he will want to select the formula best suited to the requirements of the individual infant.

Since 1911, at which time Dextri-Maltose® was introduced, physicians have turned with confidence to Mead Johnson Laboratories for the products they require to meet the nutritional needs of infants under their care. During this half-century, Mead Johnson Laboratories has worked hand-in-hand with men in pediatric research to solve the problems of infant nutrition. Thus, Mead Johnson Laboratories manifests devotion to the child by dedicating itself to the art and science of infant nutrition through research . . . *generation after generation.*

FOR "NORMAL" TERM INFANTS AND PREMATURES
ENFAMIL® / LACTUM® / DEXTRI-MALTOSE®

FOR ALLERGIC INFANTS
SOBEE® / NUTRAMIGEN®

FOR THERAPEUTIC FEEDING
PROBANA® / LOFENALAC®

Mead Johnson
Laboratories

Symbol of service in medicine

new infant formula
Enfamil®
Infant formula
nearly identical
to mother's milk[1]
in nutritional
breadth and balance
In a well-controlled institutional study[2] covering the crucial first 8 weeks of life, Enfamil produced average weight gains of 11.3 ounces every 2 weeks during the course of the study. With Enfamil, acceptance was excellent and stool patterns were satisfactory.
1. The Composition of Milks, Publication 254, National Academy of Sciences and National Research Council, Revised 1953. 2. Brown, G. W.; Tuholski, J. M.; Sauer, L. W.; Minsk, L. D., and Rosenstern, I.: J. Pediat. 56:391 (Mar.) 1960.
Mead Johnson
Laboratories
Symbol of service in medicine

Povan®

(pyrvinium pamoate, Parke-Davis)

SINGULARLY EFFECTIVE IN A SINGLE DOSE

Unlike previous therapeutic regimens which required a multiple-dose schedule, POVAN effectively controls most pinworm infections with a single dose in most cases. This outstanding vermicidal action makes it ideal, too, for preventing spread of infection in families or institutions.

POVAN is readily accepted and well tolerated. Because of its one-dose efficacy, POVAN is also favored for its reduction both of the duration and cost of treatment.

Supplied: POVAN is available in suspension or tablet form. The pleasant-tasting, strawberry-flavored suspension is supplied in 2-oz. bottles and the tablets in bottles of 25.

The suspension contains pyrvinium pamoate equivalent to 10 mg. pyrvinium base per cc. The sugar-coated tablets contain pyrvinium pamoate equivalent to 50 mg. pyrvinium base. *Dosage:* Children and adults, a single oral dose equivalent to 5 mg. per Kg. Not appreciably absorbed from the gastrointestinal tract. *Precautions:* Infrequent nausea and vomiting and intestinal complaints have been reported. Tablets should be swallowed whole to avoid staining teeth. Will color stools a bright red.

PARKE-DAVIS

PARKE, DAVIS & COMPANY, Detroit 32, Michigan

a major improvement in po

PURIVAX®
POLIOMYELITIS VACCINE

POLIOMYELITIS VACCINE, PURIFIED

MORE RAPID PROTECTION

PURIVAX Poliomyelitis Vaccine provides earlier establishment of immunity in a significant proportion of patients. Studies have shown that, after only *two* doses of the recommended three-dose series, 98 to 100 per cent of patients are immune to Type I (Parker), 97 to 100 per cent are immune to Type II, 92 to 100 per cent are immune to Type III.[1,2]

GREATER SAFETY

PURIVAX Poliomyelitis Vaccine induces high antibody titers against all three types of poliomyelitis virus. Moreover, the highly virulent Mahoney strain of Type I has been replaced by the less virulent Parker strain for even greater safety.

INCREASED PURITY

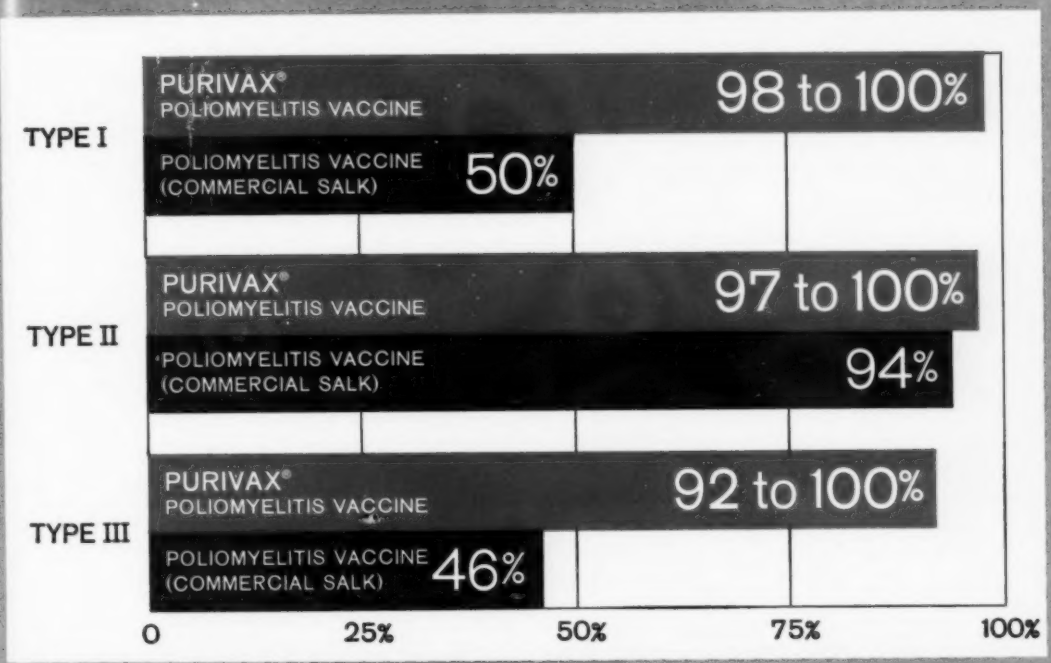
Antigen of monkey kidney origin is not detectable serologically—the possibility of allergic sensitization is thus minimized.

The high degree of purity of PURIVAX Poliomyelitis Vaccine makes possible the use of precise physical and chemical methods of standardization: each milliliter contains a uniform weight of inactivated-virus antigen.

polio immunization

After Only TWO Injections

Percentage of Patients Showing Immunity to Each Type of Poliomyelitis Virus:



Dosage and Administration: It is recommended that three injections (intramuscular or subcutaneous) of 0.5 cc. each be given, with an interval of 4 to 6 weeks between the first and second injection. The third injection should be administered 7 months or more after the second injection.

The preferred procedure is to complete immunization before the season when poliomyelitis characteristically increases. However, the vaccine may be administered throughout the summer season. Special circumstances such as exposure to the disease, tonsillectomy, or trauma are not considered contraindications.

Supplied: 2-cc. vials (4 doses).

Before prescribing or administering PURIVAX, the physician should consult the detailed information on use accompanying the package or available on request.

1. Hilleman, M. R., Charney, J., Tytell, A. A., Weihl, C., Cornfeld, D., Ichter, J. T., Riley, H. D., Jr., and Huang, N.: Investigation into the development and clinical testing of a poliomyelitis vaccine containing standardized amounts of purified poliomyelitis virus antigens, 1960 Symposium on Polio Vaccines, Newark, New Jersey, April 20, 1960.

2. Hilleman, M. R., Charney, J., Tytell, A. A., Weihl, C., Cornfeld, D., Ichter, J. T., Riley, H. D., Jr., and Huang, N.: Progress in the Development of a Purified Poliomyelitis Vaccine, presented at the Fifth International Poliomyelitis Conference, Copenhagen, Denmark, July 27, 1960.

MSD **MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., WEST POINT, PA.**

PURIVAX is a trademark of Merck & Co., Inc.

Everyday practice report:

Following initial clinical investigational work, Forhistal was sent to physicians throughout the country for evaluation as an antiallergic and antipruritic agent in everyday practice. Results in 6181 cases have now been analyzed. In 3419 cases in which a comparison was made, Forhistal was judged better than previous therapy in 7 out of 10 patients. Information about the investigational work done previously is being mailed to you separately and is also available on request.

SUPPLIED: *Tablets*, 1 mg. (pale orange, scored). *Lontabs*, 2.5 mg. (orange). *Syrup* (pink), containing 1 mg. Forhistal maleate per 5-ml. teaspoon. *Pediatric Drops* (pink), containing 0.5 mg. Forhistal maleate per 0.6 ml.

For complete information about Forhistal (including dosage, cautions, and side effects), see Physicians' Desk Reference or write CIBA, Summit, N. J.

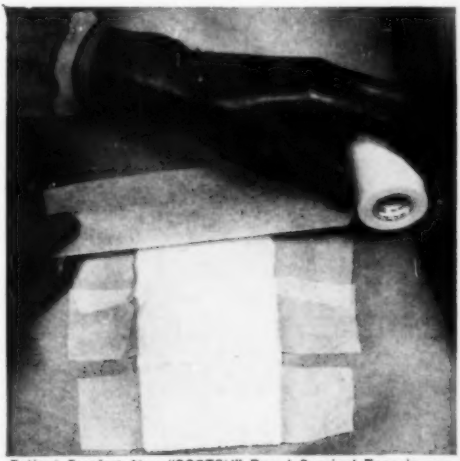
FORHISTAL® maleate (dimethpyrindene maleate CIBA)
LONTABS® (long-acting tablets CIBA)

new Forhistal® rated better than previous therapy in 7 cases out of 10

CIBA
SUMMIT, NEW JERSEY

2/2910MK-1

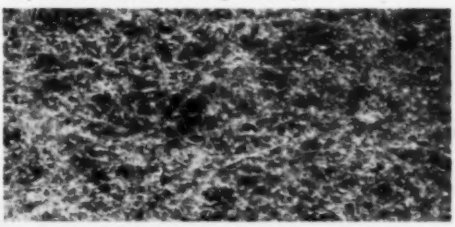
TOTALLY NEW SURGICAL ADHESIVE TAPE ANSWERS TRADITIONAL TAPE PROBLEMS

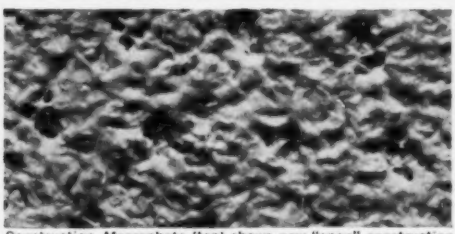


Patient Comfort. New "SCOTCH" Brand Surgical Tape is non-occlusive and physiologically inert. Prevents usual maceration . . . virtually eliminates chemical irritation, even in markedly tape-sensitive patients. It is cool, lightweight.[1]

Removal. Tissue-thin copolymer adhesive layer of "SCOTCH" Surgical Tape clings firmly to skin, yet does not entrap hairs. Tape comes off quickly and easily without depilation. Leaves no dirty residue for time-consuming "clean-up."[1]

Dressing Changes. Sticks fast, even in sitz bath or whirlpool. Fewer changes are required. Yet this tape tears with ease; does not tend to stick to rubber gloves or instruments.[1] There is no shelf deterioration, no "end-of-roll" waste.





Construction. Macrophoto (top) shows new "open" construction of "SCOTCH" Surgical Tape that allows free air passage through **microporous** backing and adhesive. Perforated tape (bottom) is almost totally occluded by thick, potentially irritating mass.[1]

"SCOTCH" Brand Surgical Tape is available through your surgical supply dealer in usual widths. ½ to 3 in., 10-yd. rolls.

REG. U.S. PAT. OFF.

SCOTCH BRAND SURGICAL TAPE MICROPOROUS

No. 530

Application. Unlike conventional adhesive tapes, "SCOTCH" Surgical Tape does not slip or "creep," and ordinarily should be laid on without tension. Where tension is desired or anticipated, shear stress on the skin may be prevented by cross strips of "SCOTCH" Surgical Tape at the ends of primary application.

MINNESOTA MINING AND MANUFACTURING COMPANY
...WHERE RESEARCH IS THE KEY TO TOMORROW

"SCOTCH" is a registered trademark of 3M Co.

1. Golden, T., A Non-Irritating, Multipurpose Surgical Adhesive Tape, Am. J. Surg. 100: 789,1960.

©3M Co., 1961

Sturdy, ***well satisfied babies***

BAKER'S MODIFIED MILK

PROVIDES OPTIMUM PROTEIN NUTRITION

"There is abundant clinical evidence . . . that formula-fed infants receiving high protein allowances compare favorably to thriving breast-fed infants."[1] Authorities,[2] whose experience with the hunger of infants fed even 3.5 grams of protein per kilogram, have opposed intakes of cows' milk which would give less protein.

Baker's Modified Milk supplies a protein level of 3.7 grams per kilogram of body weight per day to meet normal needs and to provide a dietary reserve for increased protein demands caused by fever, diarrhea and infections. An adequate water reserve is also provided for renal function and proper water balance by the 20 Cal/oz. dilution.[3]

Because an infant's health depends upon total adequacy of his diet,[4] Baker's Modified Milk supplies an optimum protein level, 6% of the calories as essential linoleic acid, and contains 7% carbohydrate composed of multiple sugars, the R.D.A.[5] of vitamins, and 7.5 mg. of iron per quart of formula.

OPTIMUM NUTRITION
Providing all the normal dietary requirements plus a reserve for stress situations while avoiding the hazards of excessive amounts of individual nutrients.

1. Hill, L. F.: J. Pediatrics 54: 545 (1959) 2. Gordon, H. H., and Ganson, A. F.: J. Pediatrics 54: 503 (1959) 3. A.A.P. Committee on Nutrition, Pediatrics 19: 339 (1957) 4. Woodruff, Calvin W.: J. A. M. A. 175: 114 (1961) 5. Recommended Dietary Allowances, NAS-NRC Publication 589 (1958) 6. U.S.P.H.S. Milk Code, Federal Security Agency Publ. 220 (1953)

Baker's MODIFIED MILK

Made only from Grade A milk[6]—scientifically formulated to duplicate the nutritional results of human milk. *Powder/Liquid*

THE BAKER LABORATORIES, INC., Cleveland 15, Ohio

diaper rash & minor skin irritations are relieved by Caldesene® ointment or powder

The happy baby likes to play with his toes, even if he can't count 'em. And if baby is subject to diaper rash and minor skin irritations — and what baby isn't? — his mother can keep him happy and protected with Caldesene.

Caldesene is a medicated, antifungal and antibacterial ointment or powder for daily routine skin care. Caldesene protects against diaper rash, prickly heat, and chafing, and relieves itching, soreness, and burning. Caldesene soothes skin irritation due to moisture, and constricting apparel, and promotes healing.

The sustained antibacterial and antifungal activity of Caldesene is due to its content of 15% calcium undecylenate. Caldesene Ointment and Powder act by forming a protective coating that prevents moisture or other irritants from coming into contact with tender or affected areas. This film created by the powder is discontinuous and does not interfere with normal tissue function. Supplied: Caldesene Powder — 2 oz. shaker containers. Caldesene Ointment — 1½ oz. collapsible tubes in a water-washable base.

Maltbie

Maltbie Laboratories Division, Wallace & Tiernan Inc., Belleville 9, New Jersey

PCD-11

Available in Canada through Elliott-Marion Company, Ltd., Montreal.

For restoring and stabilizing the intestinal flora

LACTINEX®

Mixed culture of Lactobacillus acidophilus and bulgaricus with metabolic enzymes naturally produced.

TABLETS & GRANULES

For gastrointestinal disturbances, diarrhea (antibiotic induced and others),[1,2,3] fever blisters and canker sores of herpetic origin.[4]

Usual dosage for adults and children: Four tablets or one packet of granules chewed and swallowed four times a day.

Supplied: Tablets in bottles of fifty—Granules in boxes of twelve one gram packets.

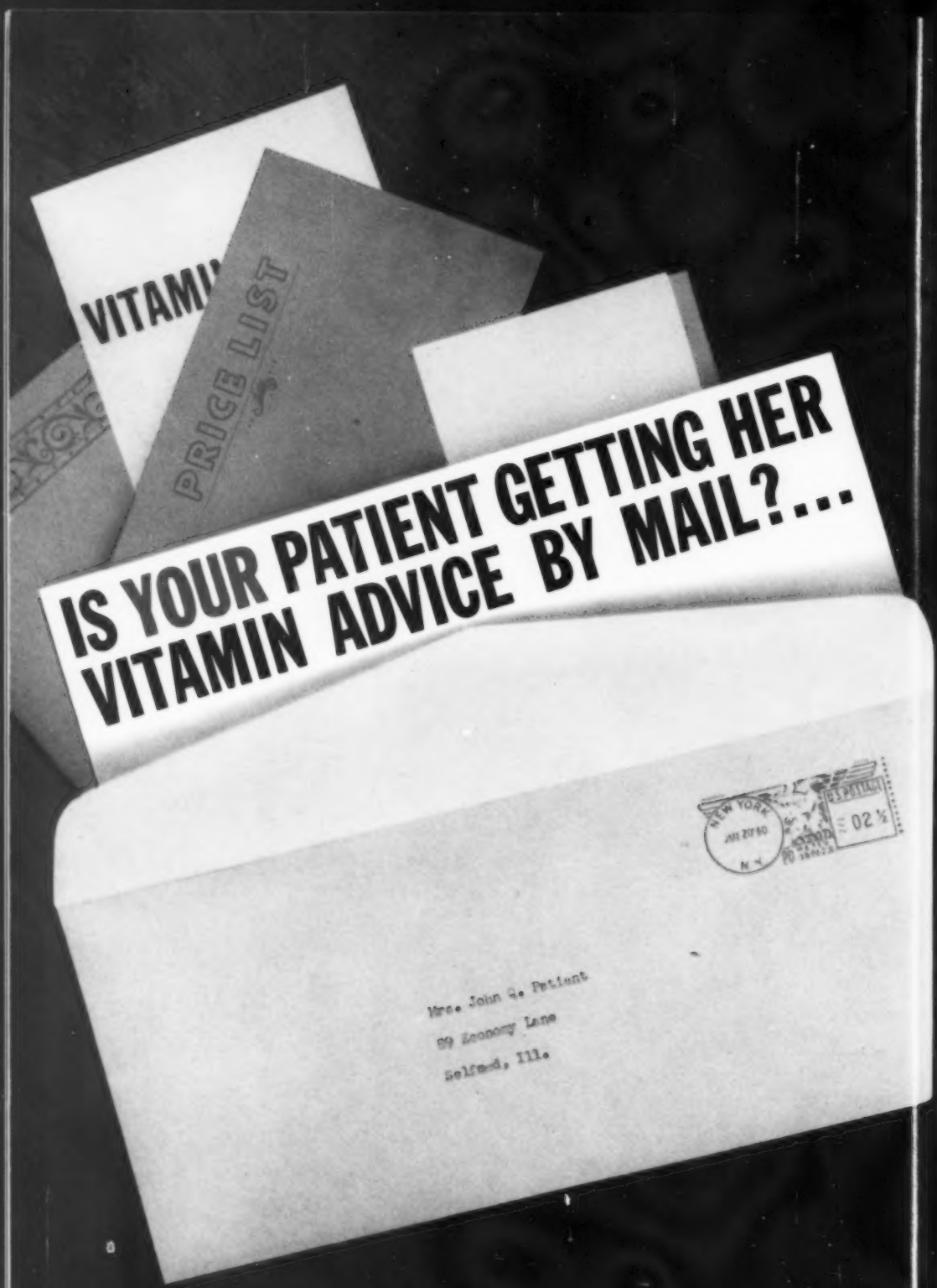
(1) Siver, Robert H.: Current Medical Digest, Vol. XXI, No. 9, September 1954. (2) McGivney, John: Texas State Journal of Medicine, Vol. 51, No. 1, January 1955. (3) Frykman, Howard M.: Minnesota Medicine, Vol. 38, No. 1, January 1955. (4) Weekes, D. J.: N. Y. State Journal of Medicine, Vol. 58, No. 16, August 1958.

HYNSON, WESTCOTT & DUNNING, INC.
Baltimore, Md.

HW&D

One of the most important problems facing the medical profession today:

Your specification versus mail order advice ▶


VITAMI
PRICE LIST
IS YOUR PATIENT GETTING HER VITAMIN ADVICE BY MAIL?...
NEW YORK
02½
Mrs. John G. Patient
89 Economy Lane
Selfmed, Ill.

don't let medical control out of your hands during the critical infant period

The rising tide of commercialism in health—by television, mail order, door-to-door salesmen—is taking medical control out of your hands during the critical newborn period. Only *you* can counter the dangers of non-professional medical advice. Mothers look to you for guidance in every step of baby's growth and development—the responsibility for the newborn's medical care is yours—yours alone.

An important way to establish your medical control early is through specification of an established ethical vitamin preparation. When prescribing for the newborn, consider the outstanding advantages of new, improved Vi-Sol® vitamins. Carefully reformulated after consideration of the recommendation of authorities,* Vi-Sol vitamins provide rational, practical, safe levels of vitamins C, D and A.

Whenever drops are outgrown, comparable improvements in levels of C, D and A are also offered the older child in Vi-Sol chewable vitamins and Vi-Sol teaspoon vitamins.

*Recommended Daily Dietary Allowances established by the National Research Council, and endorsed by the Council on Foods and Nutrition of the American Medical Association, "Vitamin Preparations As Dietary Supplements and As Therapeutic Agents," J.A.M.A. *169*:41-45 (Jan. 3) 1959.

new VI-SOL® vitamins

TRI-VI-SOL®	POLY-VI-SOL®	DECA-VI-SOL®
Vitamin Drops	Vitamin Drops	Vitamin Drops
	Teaspoon Vitamins	Teaspoon Vitamins
Chewable Vitamins	Chewable Vitamins	Chewable Vitamins
Vitamin Drops with Iron		Chewable Vitamins with Iron

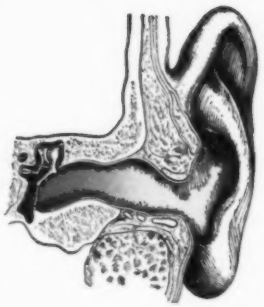
Mead Johnson Laboratories

Symbol of service in medicine

87961

three therapies of choice for infected / inflamed / painful ears

Rarely Sensitizing



1 'AEROSPORIN'® brand Otic Solution

Comprehensive bactericidal/antifungal action — eradicates *Pseudomonas* and most other common causes of otitis. Hygroscopic; restores normal acid mantle.

Each cc. contains:
'Aerosporin' brand Polymyxin B Sulfate ..... 10,000 Units
Acetic acid 1%
Propylene Glycol q.s. Sterile
Available in dropper bottles of 10 cc.

2 'CORTISPORIN'® brand Otic Drops

Broad-spectrum bactericidal action plus effective anti-inflammatory and antipruritic therapy. Eradicates most common causes of otitis; restores normal acid mantle.

Each cc. contains:
'Aerosporin' brand Polymyxin B Sulfate ..... 10,000 Units
Neomycin Sulfate ..... 5 mg.
Hydrocortisone in a sterile, slightly acid, aqueous suspension ..... 10 mg.
Available in dropper bottles of 5 cc.

3 'LIDOSPORIN'® brand Otic Solution

Acts quickly to relieve pain and itching associated with otitis externa. Bactericidal/antifungal action — eradicates *Pseudomonas* and most other common causes of otitis. Hygroscopic; restores normal acid mantle.

Each cc. contains:
'Aerosporin' brand Polymyxin B Sulfate ..... 10,000 Units
Xylocaine* HCl brand lidocaine Hydrochloride (5%) 50 mg.
Propylene Glycol q.s. Sterile
Available in dropper bottles of 10 cc.
*Reg. T.M. Astra Pharmaceutical Products, Inc. — U. S. Pat. No. 2,441,498

Literature available on request.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, N. Y.

MILK PROTEIN ALLERGY

or sensitivity to butterfat and added carbohydrate ?

In a study of 90 fussy, irritable babies, it was found that in 11% the symptoms were relieved by replacing the butterfat. An additional 30% showed an intolerance to added carbohydrate, while only 10% exhibited a milk protein allergy.[1]

Varamel, because it contains no butterfat and no added carbohydrate, makes an excellent diagnostic aid in solving cases where milk allergy is suspected. It often eliminates the need for placing the infant on a costly milk substitute, and helps to allay the mother's anxiety over her supposed milk-allergic baby.

Since Varamel is a flexible formula, the physician has complete control of the addition of carbohydrate and water.

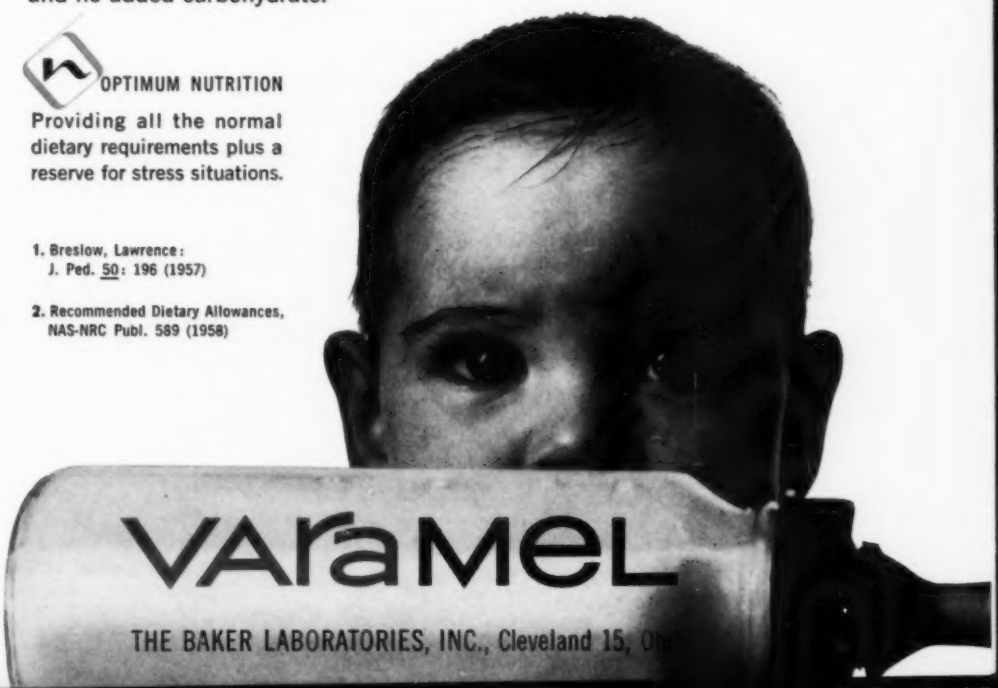
Varamel is unique: made only from Grade A milk, contains an optimum protein level, the R.D.A.[2] of iron and all essential vitamins, no butterfat, and no added carbohydrate.

OPTIMUM NUTRITION

Providing all the normal dietary requirements plus a reserve for stress situations.

1. Breslow, Lawrence: J. Ped. 50: 196 (1957)

2. Recommended Dietary Allowances, NAS-NRC Publ. 589 (1958)



Equilibrium for the epileptic

Before an epileptic child starts school, better control of seizures and the emotional support of "physician-educated" parents can help him to develop normal interpersonal relationships.

Mebaral is highly effective for most types of seizures, especially major motor seizures in children. Because it does not produce sedative daze, it does not tend to lower learning capacity.

Mebaral is unsurpassed in safety; regardless of the type of epilepsy, it is one of the best tolerated and "... least upsetting of all forms of therapy."[1] Even when Mebaral is used year after year, toxic reactions or ill effects are rare.

MEBROIN®, a synergistic combination of Mebaral and diphenylhydantoin, provides maximal control of seizures with minimal toxicity. Side effects are infrequent. Each relatively tasteless tablet contains 90 mg. of Mebaral and 60 mg. of diphenylhydantoin.

Mebaral dosage: Children under 5 years, from ¼ to ½ grain three or four times daily; over 5 years, from ½ to 1 grain three or four times daily. Adults, from 6 to 9 grains daily.

Mebroin dosage: Children under 6 years, ½ tablet once or twice daily; over 6 years, 1 tablet two or three times daily. Adults, 1 or 2 tablets three times daily (average dosage).

For epilepsy at any age

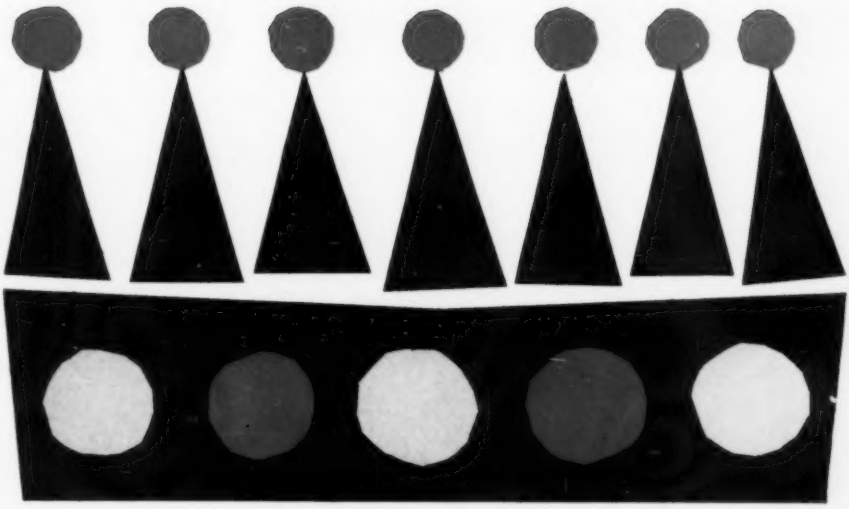
MEBARAL®

How Supplied: Mebaral tasteless tablets of 200 mg. (3 grains), 100 mg. (1½ grains), 50 mg. (¾ grain), and 32 mg. (½ grain). Bottles of 100. Mebroin virtually tasteless tablets. Bottles of 100 tablets.

1. Robertson, E. G.: *Postgrad. Med.* 25:31, Jan., 1959.

MEBARAL (BRAND OF MEPHOBARBITAL) AND MEBROIN, TRADEMARKS REG. U. S. PAT. OFF.

Winthrop LABORATORIES New York 16, N. Y.



THE CROWN OF LEADERSHIP . . . IN STEROID TOPICALS

Cort-Dome®

CREMES • LOTIONS (pH 4.6)

Micronized Hydrocortisone Alcohol in the Exclusive ACID MANTLE® Vehicle

Cort-Dome cremes and lotions are the most widely prescribed of all the steroid topicals because they offer these outstanding advantages: (a) Unique Acid Mantle Vehicle—**restores and maintains the skin's normal protective acidity and potentiates steroid activity for more prompt and predictable response at lower concentrations;** (b) Exclusive Microdispersion Process—**reduces hydrocortisone particle size to microscopic dimensions for maximum dispersion to assure therapeutic efficiency and enhanced selectivity in dosage;** (c) Wide Choice of Concentrations—**¼% strength for mild conditions and maintenance therapy; ½%, 1% and 2% strengths for more severe conditions as required;** (d) Greater Economy for Your Patient—**made possible by the increased effectiveness of lower hydrocortisone concentrations. For example, clinical experience establishes that ¼% Cort-Dome is as effective as much higher concentrations of hydrocortisone alcohol dispersed in solid, non-evaporating vehicles in a wide variety of dermatologic disorders.**

DOME CHEMICALS INC., New York 23, New York
World Leader in Dermatologicals

01061

now...prolonged antipruritic action
in a chewable tablet
for chickenpox
and other pruritic conditions

new...unique...pleasant-tasting

tacaryl T.M.

chewable tablets

METHDILAZINE, MEAD JOHNSON

prolonged antipruritic/antiallergic action...
not dependent on delayed intestinal release

Itching in children can now be controlled on b.i.d. dosage with a long-acting[1] antipruritic/antiallergic chewable tablet your pediatric patients will enjoy taking.

Tacaryl Hydrochloride is exceptionally valuable in alleviating many types of allergic and non-allergic pruritus. For example, in a group of children, 2 to 12 years of age, with atopic dermatitis, chickenpox, or contact dermatitis, 80 per cent obtained substantial or complete relief of their itching when treated with Tacaryl Hydrochloride. "No patient in this age group failed to show some degree of improvement."[2]

Tacaryl Hydrochloride is also effective in controlling symptoms in a wide variety of allergic conditions,[2-8] including hay fever and perennial rhinitis.

dosage: One Chewable Tablet (3.6 mg.) twice daily. Adjustment of dose or interval may be desirable for some patients.

contraindications: There are no known contraindications.

side effects: Drowsiness has been observed in a small percentage of patients. Dizziness, nausea, headache, and dryness of mucous membranes have been reported infrequently.

cautions: If drowsiness occurs after administration of Tacaryl Chewable Tablets or Tacaryl Hydrochloride, the patient should not drive a motor vehicle or operate dangerous machinery. Since Tacaryl Chewable Tablets or Tacaryl Hydrochloride may display potentiating properties, it should be used with caution for patients receiving alcohol, analgesics or sedatives (particularly barbiturates). Because of reports that phenothiazine derivatives occasionally cause side reactions such as agranulocytosis, jaundice and orthostatic hypotension, the physician should be alert to their possible occurrence...though no such reactions have been observed with Tacaryl Chewable Tablets or Tacaryl Hydrochloride.

supplied: Pink tablets, 3.6 mg., bottles of 100.

references: (1) Lish, P. M.; Albert, J. R.; Peters, E. L., and Allen, L. E.: Arch. internat. pharmacodyn. *129*:77-107 (Dec.) 1960. (2) Howell, C. M., Jr.: North Carolina M. J. *21*:194-195 (May) 1960. (3) Clinical Research Division, Mead Johnson & Company. (4) Wahner, H. W., and Peters, G. A.: Proc. Staff Meet. Mayo Clin. *35*:161-169 (March 30) 1960. (5) Crepea, S. B.: J. Allergy *31*:283-285 (May-June) 1960. (6) Crawford, L. V., and Grogan, F. T.: J. Tennessee M. A. *53*:307-310 (July) 1960. (7) Spoto, A. P., Jr., and Sieker, H. O.: Ann. Allergy *18*:761-764 (July) 1960. (8) Arbesman, C. E., and Ehrenreich, R.: New York J. Med. *61*:219-229 (Jan. 15) 1961.

MARCH, 61 347861

Mead Johnson Laboratories

Symbol of service in medicine

Cremomycin® provides rapid relief of virtually all diarrheas

NEOMYCIN—actively bactericidal against a wide range of gram-negative intestinal pathogens, but relatively ineffective against certain diarrhea-causing organisms.

SULFASUXIDINE®, succinylsulfathiazole—an ideal adjunct to neomycin because it is highly effective against Clostridia and certain other neomycin-resistant organisms.

KAOLIN AND PECTIN—coat and soothe the inflamed mucosa, adsorb toxins, help provide rapid symptomatic relief.

Additional information on CREMOMYCIN is available to physicians on request.

MSD MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., WEST POINT, PA.

CREMOMYCIN AND SULFASUXIDINE ARE TRADEMARKS OF MERCK & CO., INC.

the iron you can depend on

for continued effectiveness

- *clinical effectiveness confirmed*[1]
- *palatable–free from astringency*
- *well tolerated even between meals*
- *easily mixed with formula, milk, juices*
- *does not stain teeth*

the drop dose form

CHĒL-IRON®

Brand of Ferrocholinate*

PEDIATRIC DROPS

(25 mg. iron/cc.)

the teaspoon dose form

CHĒL-IRON®

Brand of Ferrocholinate

LIQUID

(50 mg. iron/tsp.)

because it's chelated Chēl-Iron offers optimal assurance of effective therapy for more of your patients. Because it is neither ionized nor precipitated after ingestion, Chēl-Iron rarely causes the gastrointestinal complaints often experienced with nonchelated iron salts, such as ferrous sulfate or ferrous gluconate.[1,2] Thus, your supplemental or therapeutic iron regimen is uninterrupted, and full hematologic benefits are *maintained*.

1. Franklin, M., et al.: J.A.M.A. 166:1685, 1958. 2. A.M.A. Council on Drugs: New and Nonofficial Drugs 1960, Philadelphia, Lippincott, 1960, p. 521.

*U.S. Pat. 2,575,611

PEDIATRIC PRODUCTS

KINNEY & COMPANY, INC.

Columbus, Indiana

PROMPTLY ANSWERS THE CALL

for relief of nausea and vomiting

EMETROL®

Phosphorated Carbohydrate Solution

Make your first thought EMETROL—whenever an antiemetic is indicated, as in acute infectious gastroenteritis or intestinal "flu," and in the prevention or treatment of nausea due to drug therapy or motion sickness.

EMETROL quickly controls most cases of functional nausea and vomiting without risk of untoward effects or masking of serious organic pathology.

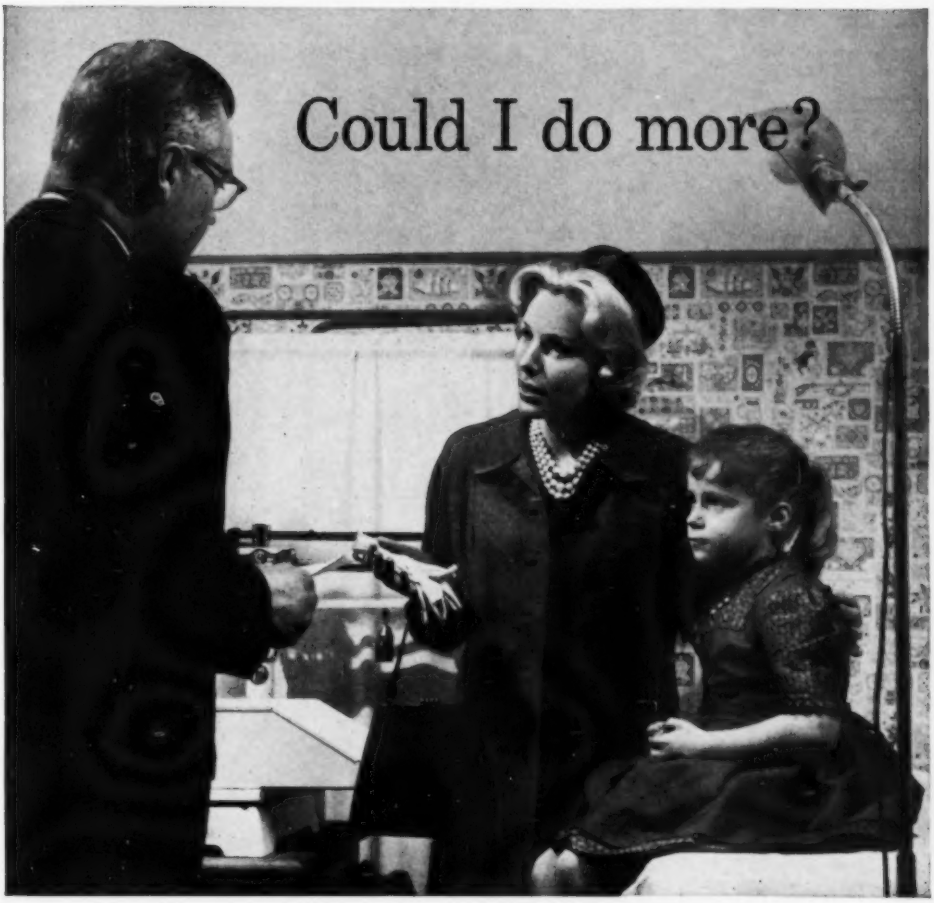
Supplied: Bottles of 3 fl.oz. and 16 fl.oz. through all pharmacies.

EMETROL Bibliography: 1. Bradley, J. E., et al.: J. Pediat. 38:41, 1951. 2. Proutt, L. M., et al.: Bull. School Med. Univ. Maryland 36:86, 1951. 3. Levenstein, I.: Report of Leberco Laboratories, Roselle Park, N. J. 4. Bradley, J. E.: Mod. Med. 20:71, No. 20, 1952. 5. Tebrock, H. E., and Fisher, M. M.: M. Times 82:271, 1954.

in clinical use for 10 years... not a single report of side effects

PEDIATRIC PRODUCTS

KINNEY & COMPANY, INC. Columbus, Indiana



In nutritional anemia naturally nutritious oatmeal is high in iron—high in protein and Vitamin B_1

Quaker Oats and Mother's Oats are the same fine product.

When you recommend hot Oatmeal, the days begin with good nutrition. Oatmeal is high in natural nutritional elements, especially protein, iron, phosphorus and vitamin B_1.

The iron content in Oatmeal will help build hemoglobin and red blood cells, while the high quality protein contributes to an adequate diet that will help build up resistance to disease.

One ounce of Quaker Oats provides the following percentages of adult M.D.R.: Thiamine (vitamin B_1) 16.5%, phosphorus 16.5%, and iron 11.0%. Each ounce also provides 110 calories, and 16.7% protein, 6.9% fat, 62.4% carbohydrates, and 1.5% non-nutritive crude fiber.

The Quaker Oats Company

CHICAGO 54, ILLINOIS

the best guarded vitamins in the world...

112 COATINGS guard the vitamins in each VIACETS Candisphere to assure you and your little patients of utmost stability and freshness. No vitamin "escape" until the Candispheres are chewed and ready to go to work. **75 DAYS** of meticulous processing create a vitamin preparation you can depend on for highest quality and uniform potency. **5 FLAVORS** in each package will please every pediatric palate; cherry, raspberry, orange, lemon and lime (in 5 dazzling colors). With VIACETS, vitamin time is really treat time! So prescribe these tasty Candispheres for your patients today.

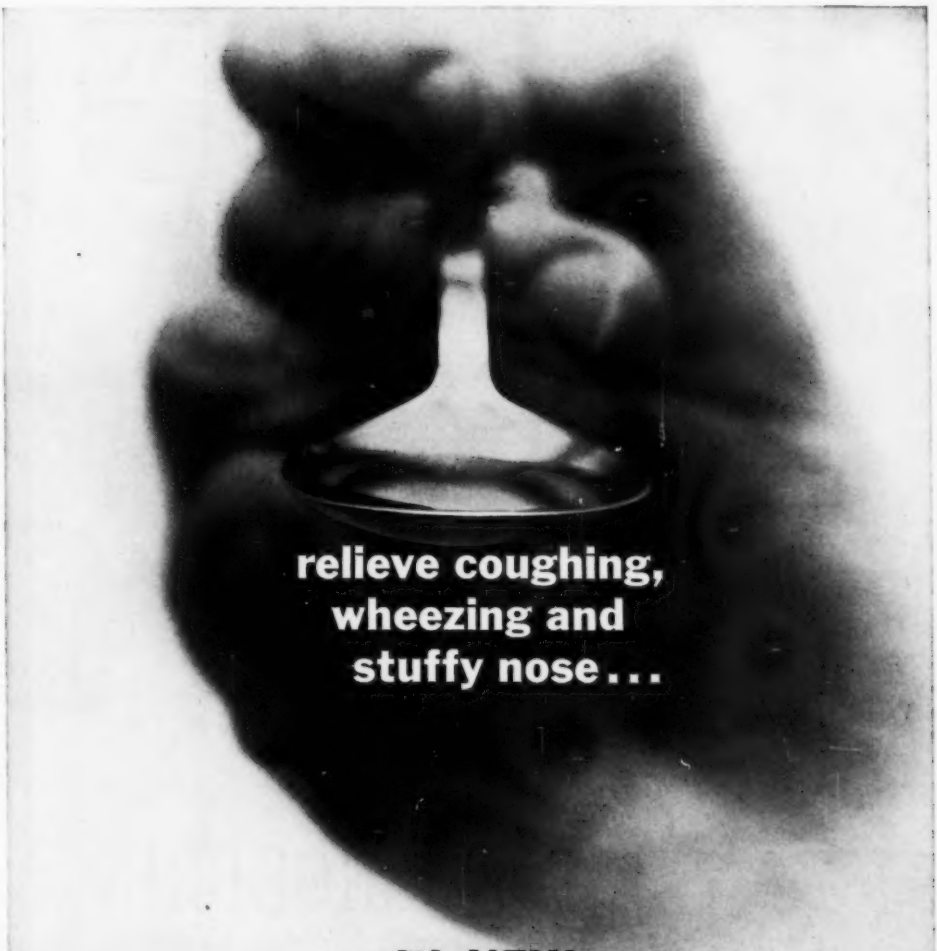
DELICIOUS · CHEWABLE · MULTIVITAMIN CANDISPHERES®

Each VIACETS Candisphere contains: Vitamin A, 5,000 U.S.P. Units; Vitamin D, 1,000 U.S.P. Units; Vitamin E, 1.0 I.U.; ascorbic acid, 50 mg.; thiamine mononitrate, 1.0 mg.; riboflavin, 1.0 mg.; pyridoxine, 1.0 mg.; calcium pantothenate, 1.0 mg.; niacinamide, 5.0 mg.; Vitamin B_{12}, 2.0 mcg.; folic acid, 0.1 mg. **Dosage:** One or two VIACETS daily. **Supply:** Bottles of 120 multicolored candispheres. **P. S. — For patients needing only Vitamins A, D, and C: delicious, orange-flavored chewable Adcets® Candispheres.** Literature available to physicians on request.

VIA-61-1

Viacets

WALKER LABORATORIES, INC.
MOUNT VERNON, NEW YORK



with NEW

'ACTIFED-C' brand EXPECTORANT

ANTITUSSIVE · EXPECTORANT · BRONCHODILATOR · DECONGESTANT · ANTIHISTAMINIC

The etiology of cough is such that drug therapy designed to produce relief may be called upon to provide several therapeutic actions simultaneously. The ingredients of 'Actifed-C' Expectorant were selected because they produce desirable antitussive, expectorant, bronchodilator, decongestant and antihistaminic effects.

Each 5 cc. teaspoonful contains:

'Actidil'® brand Triprolidine Hydrochloride	2 mg.
'Sudafed'® brand Pseudoephedrine Hydrochloride	30 mg.
Codeine Phosphate	10 mg.
Glyceryl Guaiacolate	100 mg.

Dosage: Adults and children over 12 years—2 tsp., 4 times daily. Children 6 to 12 years—1 tsp., 4 times daily. Infants and children up to 6 years—½ tsp., 4 times daily.

Precaution: Although pseudoephedrine hydrochloride causes virtually no pressor effect in normotensive patients, it should be used with caution in patients with hypertension. In addition, even though triprolidine hydrochloride produces only a low incidence of drowsiness, appropriate precautions should be observed.

BURROUGHS WELLCOME & CO. (U.S.A.) INC., Tuckahoe, New York

■ taste-tested
and approved
by children
for children

HOMICEBRIN®

homogenized multiple vitamins

Willful youngsters are often quite particular about their personal vitamin supplement. However, even the most fastidious of them welcome pleasant-tasting Homicebrin into their daily routine.

This boon to harried parents is also reassuring to the physician. Homicebrin supplies eight essential vitamins, potency-protected by homogenization and careful buffering. To be certain your "tot-age" patients take and receive their full vitamin requirements, specify Homicebrin.

Homicebrin® (homogenized multiple vitamins, Lilly)

Lilly Vitamins . . . "The Physician's Line"

103003

They BOUNCE back fast with TYLENOL®

she's flying high now... her temperature and discomfort brought under control quickly with Tylenol®

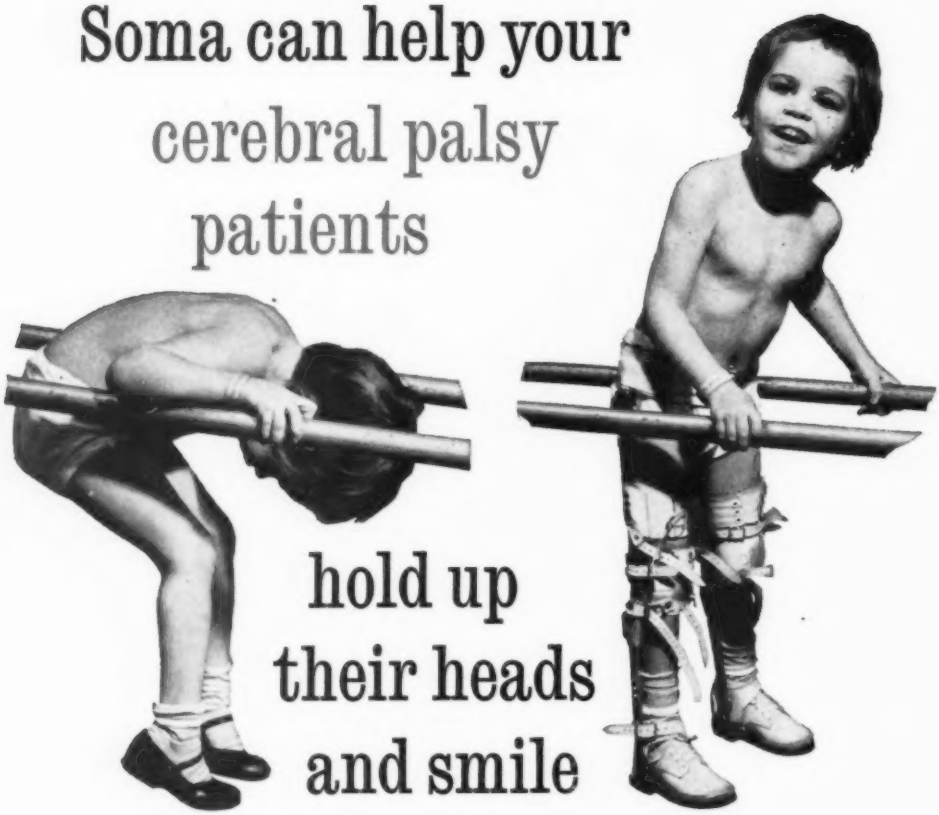
TYLENOL® acetaminophen an effective pediatric antipyretic and analgesic[1]
remarkably free from toxicity[2]
well accepted, well tolerated by children[1]

TYLENOL ELIXIR—120 mg. (2 gr.) per 5 cc.; 4 and 12 fl. oz. bottles.
TYLENOL DROPS—60 mg. (1 gr.) per 0.6 cc.; 15 cc. bottles with calibrated droppers.

McNEIL McNEIL LABORATORIES, INC.
PHILADELPHIA 32, PA.

1. Cornely, O. A., and Ritter, J. A.: N-acetyl-p-aminophenol (Tylenol Elixir) as a Pediatric Antipyretic-Analgesic, J.A.M.A. 160:1219 (Apr. 7) 1956.
2. Mintz, A. A.: Management of the Febrile Child, J. Ky. Acad. Gen. Pract. 5:26 (Jan.) 1959.

Soma can help your cerebral palsy patients



hold up their heads and smile

Muscle-relaxing, pain-relieving Soma speeds up habilitation . . . encourages children to want to help themselves

Soma hastens small successes so important to C.P. patients. Children are happier—more willing to walk, dress, feed themselves.

Physical therapy is more beneficial. Patients wear corrective braces with less discomfort[1]—undergo muscle stretching more easily.[2] They drool less. Soma is notably safe. Drowsiness occurs infrequently. Dosage: Children over 5, one 250 mg. capsule 2 or 3 times a day.

Literature and samples on request. Also available: 15-minute documentary color film by Dr. C. A. Spears.

1. Phelps, P. M., Arch. of Ped., 76:243-250, June, 1959.
2. Spears, C. A., Annals of N.Y. Acad. of Sc., Mar. 30, 1960, Vol. 86.

SOMA®

(*carisoprodol, Wallace*)

Wallace Laboratories, Cranbury, New Jersey

Schering

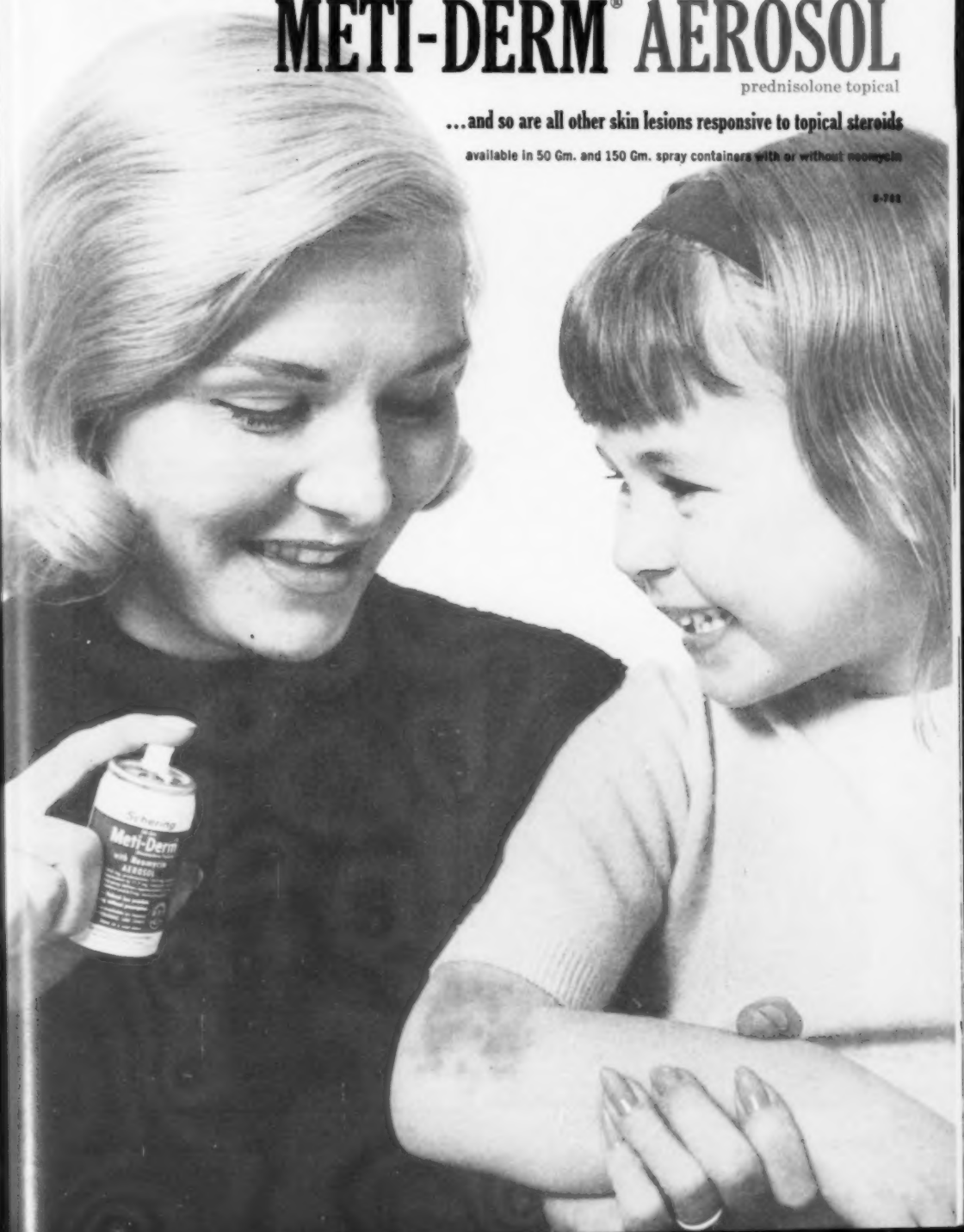
infantile eczemas, big problem of little patients, controlled with METI-DERM® AEROSOL

prednisolone topical

...and so are all other skin lesions responsive to topical steroids

available in 50 Gm. and 150 Gm. spray containers with or without neomycin

8-761



CENTER LABS' ALLERGENS

assure diagnostic and therapeutic success

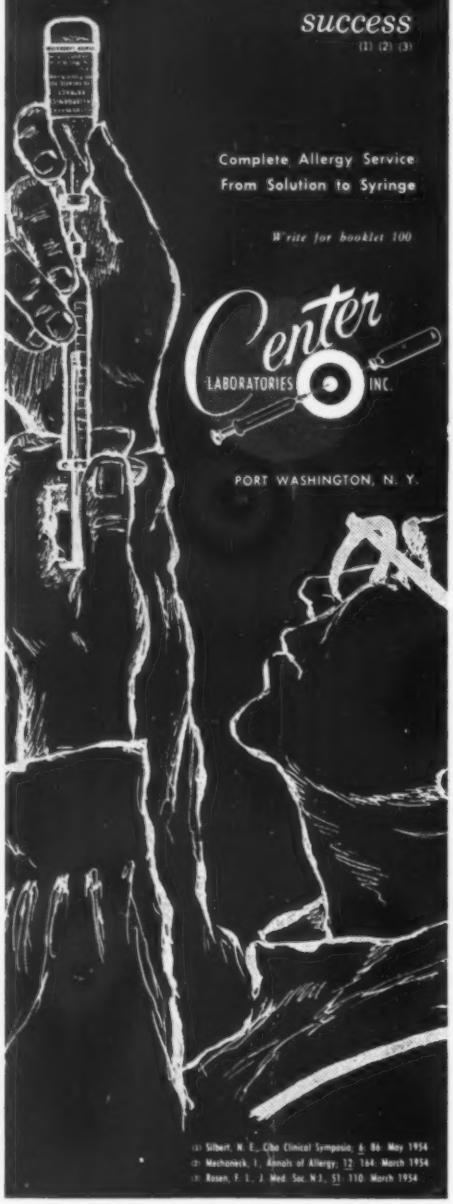
(1) (2) (3)

Complete Allergy Service
From Solution to Syringe

Write for booklet 100

Center LABORATORIES INC.

PORT WASHINGTON, N. Y.



(1) Silbert, N. E., Clin Clinical Symposia, 6: 86. May 1954
(2) Mechaneck, I., Annals of Allergy, 12: 164. March 1954
(3) Rosen, F. L., J. Med. Soc. N.J., 51: 110. March 1954

Viokase Pancreatin 4 times N.F. minimum potency standards.

VIOKASE

WHOLE PANCREAS
Not an extract!

EFFECTIVE substitution therapy in demonstrated pancreatic deficiency.
Powder and Tablets

NOT ENTERIC COATED

Shwachman, H., The Child in Health and Disease, Grulee and Eley, 2nd Edit.

Shwachman, H. and Leubner, H., Advances in Pediatrics, VII, 249, 1955.

Kagan, B. M., Illinois Medical Journal, 107, 120, 1955.

Kumar, B. B., and Gibbs, G. E. A.M.A. Journal Diseases of Children, 91:606, 1956.

Literature on request.

VIOBIN, Monticello, Illinois

with **your** support

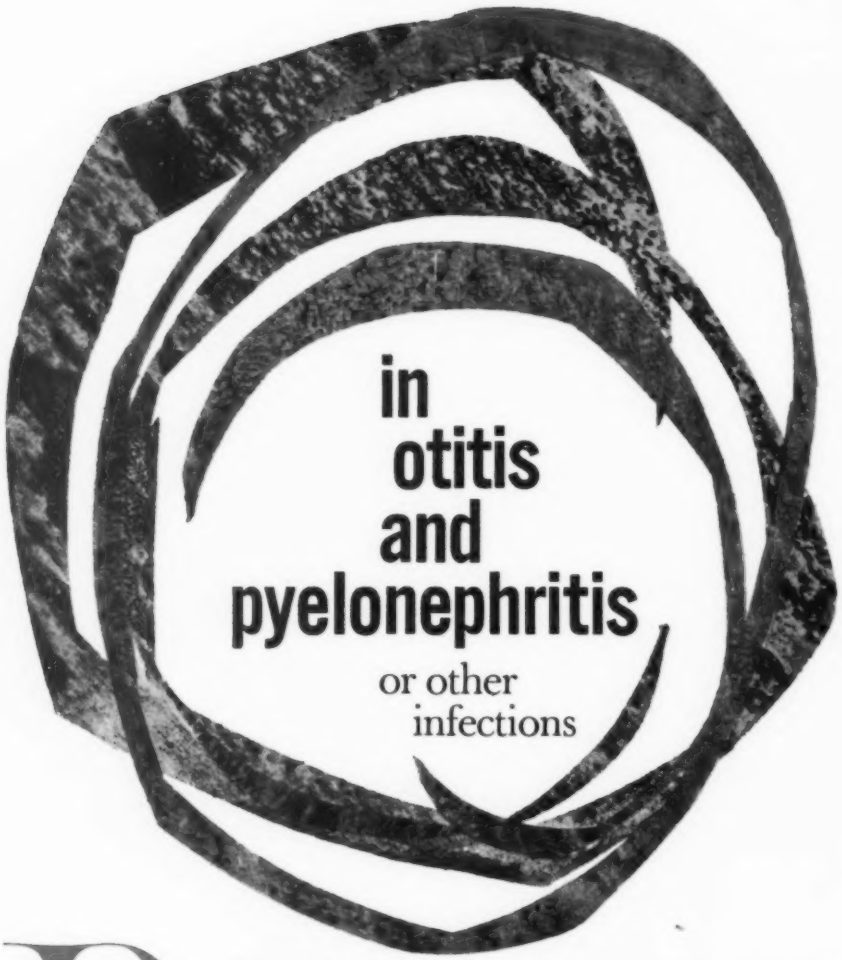
RETARDED
CHILDREN
CAN BE
HELPED

combating bacterial infections in children? ***consider these 8 clinically significant advantages of TERFONYL® Squibb Triple Sulfas (Trisulfapyrimidines) in highly palatable suspension***

TERFONYL rarely causes superinfection TERFONYL soluble in urine at varying pH TERFONYL minimal disturbance of intestinal flora TERFONYL rarely sensitizes TERFONYL effective against wide range of gram-positive and gram-negative pathogens TERFONYL diffuses rapidly through tissues TERFONYL readily crosses blood-brain barrier TERFONYL sustains therapeutic blood levels and TERFONYL is economical, too. Supply: Suspension, raspberry flavored, 0.5 Gm. per teaspoonful (5cc.). Also Tablets, 0.5 Gm. Each teaspoonful, each Tablet, provides 0.167 Gm. each of sulfadiazine, sulfamerazine, and sulfamethazine. For full information see your Squibb Product Reference or Product Brief.

SQUIBB *Squibb Quality—the Priceless Ingredient*

Terfonyl® is a Squibb trademark



antibiotic therapy with an added measure of protection

DECLOMYCIN®

DEMETHYLCHLORTETRACYCLINE LEDERLE

against relapse—up to 6 days' activity on 4 days' dosage
against secondary infection—sustained high activity levels
against "problem" pathogens—positive broad-spectrum antibiosis

CAPSULES, 150 mg., 75 mg.; PEDIATRIC DROPS, 60 mg./cc.; SYRUP, 75 mg./5 cc.

Request complete information on indications, dosage, precautions and contraindications from your Lederle representative or write to Medical Advisory Department.

LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, New York

Optimal Asthma Relief

from smallest dosage...

in briefest time

Medihaler®

automatically controlled dosage by aerosol administration

22½% more vital capacity within seconds

The suspension of premicronized dry particles assures maximum delivery of the medication to the alveolar spaces where the therapeutic effect is exerted. The Medihaler suspension affords 5 times the bronchodilating power of the same medication in solution and approximately 20 times that of a squeeze bulb nebulizer.

Medihaler is available with either of the two outstanding bronchodilating agents:

Medihaler-ISO® (isoproterenol)

Medihaler-EPI® (epinephrine)

NEW! 30 cc size vial for office or home

Riker Northridge, California

when
he's
ready
for
cereals...

PABLUM®
BRAND

your
guidance
is
still
important

Mother looks for your guidance

"Cereal is an excellent food to offer the baby who has a large appetite early in life and is not satisfied with the calories provided by his intake of milk."[1] When to start and what cereal to choose for baby? These are important questions for a mother. Your guidance is as important now as when you prescribed baby's first formula.

Five tasteful varieties—Rice, Mixed, Oatmeal, Barley and High Protein—help with important taste-training and feeding patterns. In addition to calories, PABLUM Cereals provide protein, carbohydrate, vitamins, and important minerals—especially iron. They are formulated especially to help meet the infant's nutritional needs when he graduates to solid foods.

Baby needs your guidance

Because rice is hypoallergenic,[2] PABLUM Rice Cereal is well suited to the allergic infant.

PABLUM High Protein Cereal is useful when the diet requires added protein. It has been noted that "addition of PABLUM to infants' diets considerably increased the amount of fluorine ingested"[3]—an important consideration for caries prevention.

When you specify PABLUM, you are sure of safe, sound, nutritious cereals for baby's early years.

Specified by physicians for nearly 30 years.

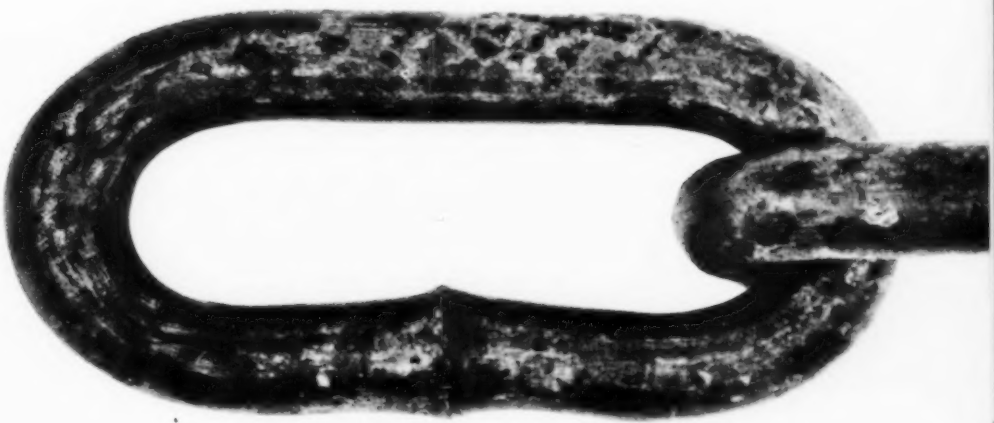
References: (1) Bartram, J. B., in Nelson, W. E.: Textbook of Pediatrics, ed. 7, Philadelphia, W. B. Saunders Company, 1959, p. 128. (2) Benson, R. A., and Kimball, F. T.: Arch. Pediat. *64*:476, 1947. (3) Ham, M. P., and Smith, M. D.: J. Nutrition *53*:215, 1954.

43141

Edward Dalton Co.
A DIVISION OF
MEAD JOHNSON & COMPANY

Quality products from nutritional research

There is an increasing awareness of iron deficiency in infants and children



Now...two new products to supply the iron they need at the ages they need it

There is an increasing awareness of iron deficiency in infants and children

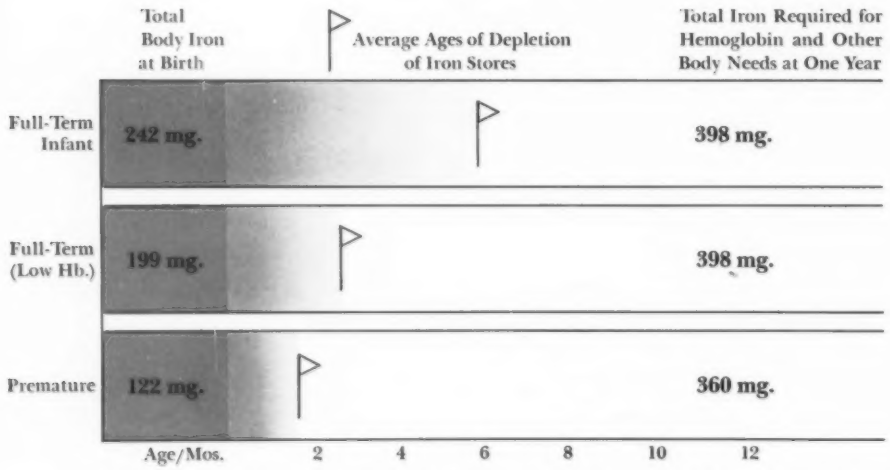
"Iron deficiency anemia is the most common deficiency disease of infancy and childhood."[1]

"The average full-term infant requires 8 mg. of iron daily from about 6 months of age...."[2]

The older child, too, often is in a precarious state of iron balance "...because of his added needs to support growth and his expanding blood volume...."[3]

The following chart shows the ages at which iron stores of the newborn infant tend to become depleted and the total iron needed by the end of the first year. To help fill the gap, prophylactic iron should be started at 2 to 6 months of age.

WHEN IRON STORES BECOME DEPLETED[2]



References: (1) Jacobs, I.: GP *21*:93 (Jan.) 1960. (2) Shulman, I.: J.A.M.A. *175*:118-123 (Jan. 14) 1961. (3) Moore, C. V., in Wohl, M. G., and Goodhart, R. S.: Modern Nutrition in Health and Disease, ed. 2, Philadelphia, Lea & Febiger, 1960, p. 243.

Mead Johnson Laboratories

Symbol of service in medicine

Now...two new products to supply the iron they need at the ages they need it

TRI-VI-SOL®

VITAMIN DROPS WITH IRON

DECA-VI-SOL®

CHEWABLE VITAMINS WITH IRON

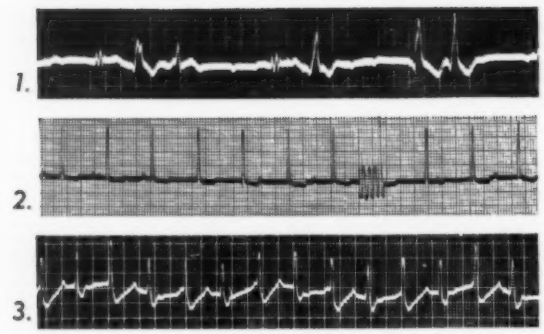
These two new formulations—one for infants, one for older children—are distinctive additions to the present line of Vi-Sol® vitamins, thereby providing the choice of Tri-Vi-Sol drops with and without iron and Deca-Vi-Sol chewable vitamins with and without iron. Both new products taste good. The packaging carefully limits elemental iron to a total of 500 mg. per bottle. Nevertheless, the bottles should be kept out of the reach of children.

Tri-Vi-Sol vitamin drops with iron. **Each 0.6 cc. daily dose supplies 10 mg. elemental iron plus safe, rational amounts of vitamins C, D and A. Supplied in bottles of 30 cc.**

Deca-Vi-Sol chewable vitamins with iron. **Each chewable tablet supplies 10 mg. elemental iron and safe, rational amounts of C, D and A plus seven significant B vitamins. Supplied in bottles of 50 chewable tablets.**

10 mg. of prophylactic iron... logically combined for your convenience with two of the most widely used and accepted pediatric vitamin products

27161



*Are you confident you could interpret these tracings?**

Here's authoritative guidance for the non-cardiologist in the diagnosis and treatment of cardiac arrhythmias

Ready This Month! **Phibbs**

THE CARDIAC ARRHYTHMIAS

A Guide for the General Practitioner

This new book is a straightforward and unsophisticated presentation of electrocardiographic interpretation of the more common cardiac arrhythmias. With its help, all physicians who are not cardiologists can gain a real understanding of the subject and develop confidence in their ability to diagnose and treat most cardiac arrhythmias. Dr. Phibbs' new book reduces the facts of electrocardiographic diagnosis to a kind of "basic English": it integrates a few, well chosen words with nearly 150, large "atlas-type" anatomic drawings and electrocardiographic tracings like the ones above to clarify the differences between functional and pathological arrhythmias in a way that has not been attempted before. This new book describes the sequence of events in normal and abnormal heart mechanisms. You'll find 50 practice problems in the back of the book to help you develop your skills in interpreting these tracings.

By BRENDAN PHIBBS, M.D., Casper Clinic, Casper, Wyoming. Ready this month. Approx. 128 pages, 6¾" x 9¾", illustrated. About $6.75.

***Answers:**

1. ***Complete atrioventricular block with multiple ventricular pacemakers.***
2. ***Interference-dissociation with atrioventricular block.***
3. ***Flutter (3:2 ratio).***

(All tracings shown above appear 30% larger in the book.)

Order on 30 Day Approval from

The C.V. MOSBY Company
3207 Washington Blvd., St. Louis 3, Mo.

I INDIVIDUAL
P PATIENT
S SAFETY

DISPOSABLE UNITS
FOR MALE AND FEMALE
INFANTS

Sterilon

PEDIATRIC URINE COLLECTORS

. . . fit infants of either sex, staying in place by means of pressure sensitive adhesive, cannot leak or spill, may be worn under diaper, guaranteed non-toxic and non-irritating.

Sterilon PUC-10: For collecting samples or ascertaining volume over short periods. Self-sealing top makes bag a leak-proof container for transporting urine for laboratory examination.

Sterilon PUC-24: For obtaining accurate collection over a 24-hour period. Set includes 4-foot connecting tube.

Stock Nos. PUC-10 and PUC-24. Clean and ready to use for normal collections.

Stock Nos. PUC-10-S and PUC-24-S. Packed sterile for collecting sterile specimens.

QUALITY IS OUR CORNERSTONE

Sterilon CORPORATION
500 Northland Ave., Buffalo 11, N. Y.

Sterilon Laboratories
Fayette, Ala.

Sterilon of Canada Ltd.
Niagara Falls, Ont.

Quality with Economy

Clinically proved oral penicillin therapy that costs your patients less

PENTIDS

Squibb Penicillin G Potassium

Available in these convenient dosage forms: Pentids '400' Tablets (400,000 u.) • Pentids '400' for Syrup (400,000 u. per 5 cc. when prepared) • Pentids Tablets (200,000 u.) • Pentids for Syrup (200,000 u. per 5 cc. when prepared) • Pentid-Sulfas Tablets (200,000 u. with 0.5 Gm. triple sulfas) • Pentid-Sulfas for Syrup (200,000 u. with 0.5 Gm. triple sulfas per 5 cc. when prepared) • Pentids Capsules (200,000 u.) • Pentids Soluble Tablets (200,000 u.)

For full information, see your Squibb Product Reference or Product Brief.

SQUIBB

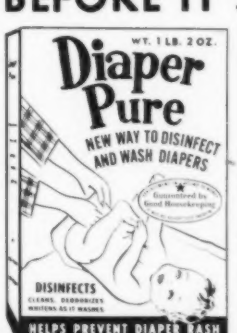
Squibb Quality—the Priceless Ingredient

"PENTIDS"® AND "PENTID"® ARE SQUIBB TRADEMARKS.

PEDIATRICIAN

Associate desired for an expanding health plan medical group; new Clinic and Hospital facilities; annual vacation study allowances; retirement pension program; minimum salary $15,000 annual guarantee, second year $18,000, third year $20,000 and partnership after mutually satisfactory association; Board eligibility or certification required; financial arrangements available for interview of seriously interested applicants. Send full details of training and experience in first letter to: Charles Varga, M.D., Chairman, Clinic Committee, The Permanente Clinic, Bess Kaiser Hospital, 5055 N. Greeley Avenue, Portland 17, Oregon.

STOP DIAPER RASH BEFORE IT STARTS



DIAPER PURE

- Used in diaper pail and in daily washing.
- Ends use of borax and separate quaternary ammonia rinses.
- Whitens without boiling or bleaching.
- Disinfects, cleans, and deodorizes.

AT DRUG AND FOOD STORES

1 package washes and treats 300 diapers.

INGREDIENTS: Active: Trisodium Phosphate 3.5%, Sodium Metasilicate 3.5%, Triethanolamine Oleate .30%, Para diisobutyl phenoxy ethoxy ethyl dimethyl benzyl ammonium chloride monohydrate .25%. Bacterially inert ingredient 92.45%

Physicians' samples on request

CENTRAL DRUG

18 Stetson St. Buffalo 6, N. Y.

Schering

"The experience to date with griseofulvin has been so promising for the management of *Microsporum audouini*, *Trichophyton tonsurans* and *Trichophyton violaceum* that it has become the treatment of choice for these infections of the scalp."[1]

oral **fulvicin**® griseofulvin

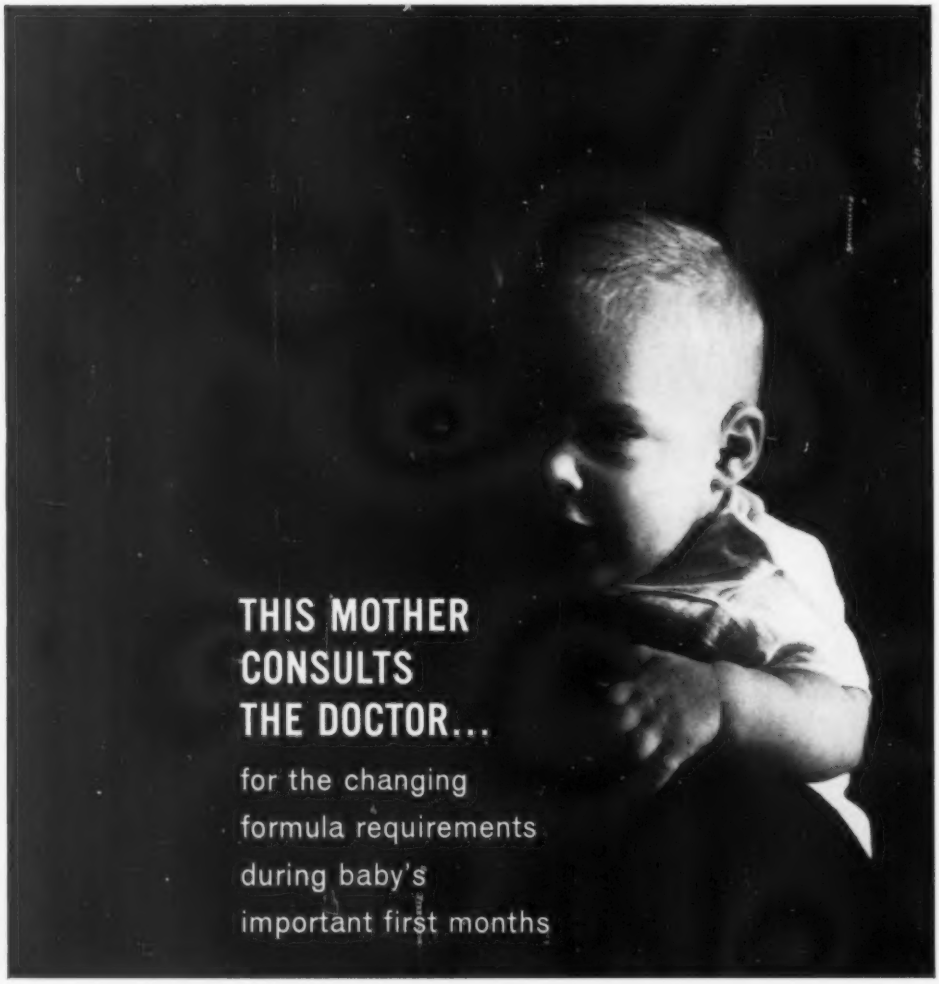
Supplied: FULVICIN Tablets (scored), 500 mg., in bottles of 20 and 100; 250 mg., in bottles of 30, 100 and 500. *Reference:* Sulzberger, M. B., *et al.*: Dermatology: Diagnosis and Treatment, ed. 2, Chicago, Year Book Publishers, 1961, p. 350. For complete details, consult latest Schering literature available from your Schering Representative or Medical Services Department, Schering Corporation, Bloomfield, N. J.

SCHERING CORPORATION • BLOOMFIELD, NEW JERSEY

S-826

***Tinea capitis due to* T. tonsurans *cleared after 7 weeks of therapy with* FULVICIN.**

FROM WEINER, M. A.; GOULD, A. N., AND GANT, J. O., JR.: GRISEOFULVIN IN RINGWORM INFECTIONS. SCIENTIFIC EXHIBIT PRESENTED AT A.M.A. CLINICAL MEETING, DECEMBER, 1960, WASHINGTON, D. C.



"from Contented Cows"

THE DOCTOR PRESCRIBES *the dilution and carbohydrate adjustment for each baby's needs, with Carnation–the flexible formula milk.*

THE DOCTOR DECIDES *the proper time and amounts of iron, Vitamin C and other supplementation for each individual.*

THE BABY THRIVES–*as babies have for generations on natural cow's milk in its soft-curd form, with protein and other nutrients at levels proven adequate by 30 years of successful feeding with the Carnation Evaporated Milk formula.*

Ready-prepared, for convenience. Carnalac is Carnation Evaporated Milk with its added Vitamin D, plus carbohydrate. The mother just adds water. Diluted 1:1, Carnalac provides 2.8% protein, 7.1% carbohydrate, 3.2% fat, 400 I. U. Vitamin D per reconstituted quart, 20 calories per fluid ounce.

GANTRISIN:
A SULFONAMIDE OF CHOICE FOR THE ROUTINE TREATMENT OF COMMON CHILDHOOD INFECTIONS. EFFECTIVE AGAINST A WIDE RANGE OF GRAM-POSITIVE AND GRAM-NEGATIVE BACTERIA, SAFE EVEN IN PROLONGED USE. GANTRISIN IS AVAILABLE IN A VARIETY OF PALATABLE PEDIATRIC FORMS—IN DELICIOUS FLAVORS READILY ACCEPTED BY THE FUSSIEST OF YOUR LITTLE PATIENTS...

THE SULFONAMIDE OF CHOICE **IN FLAVORS A CHILD WOULD CHOOSE**

GANTRISIN
PEDIATRIC SUSPENSION
(raspberry flavored)
SYRUP
(chocolate flavored)

LIPO GANTRISIN
(vanilla-mint flavored)

Packages: GANTRISIN: *Pediatric Suspension:* Each teasp. (5 cc) provides the equivalent of 0.5 Gm Gantrisin, raspberry flavored—bottles of 4 oz and 16 oz. *Syrup:* Provides the equivalent of 0.5 Gm Gantrisin per teasp. (5 cc), chocolate flavored—bottles of 4 oz and 16 oz.

LIPO GANTRISIN (the long-acting form of Gantrisin): Provides the equivalent of 1.0 Gm Gantrisin per teasp. (5 cc), vanilla-mint flavored homogenized mixture—bottles of 4 oz and 16 oz.

Consult literature and dosage information, available on request, before prescribing.

GANTRISIN®—brand of sulfisoxazole

ROCHE
ROCHE
LABORATORIES
Division of Hoffmann-La Roche Inc.

are opiates now outmoded in pediatric diarrhea?

Entoquel™ syrup

(Thihexinol methylbromide)

the first pharmacologically-specific, non-narcotic antiperistaltic agent ■ controls diarrhea as rapidly and effectively as opiates ■ without the undesirable properties of opiates ■ pleasant butterscotch flavor

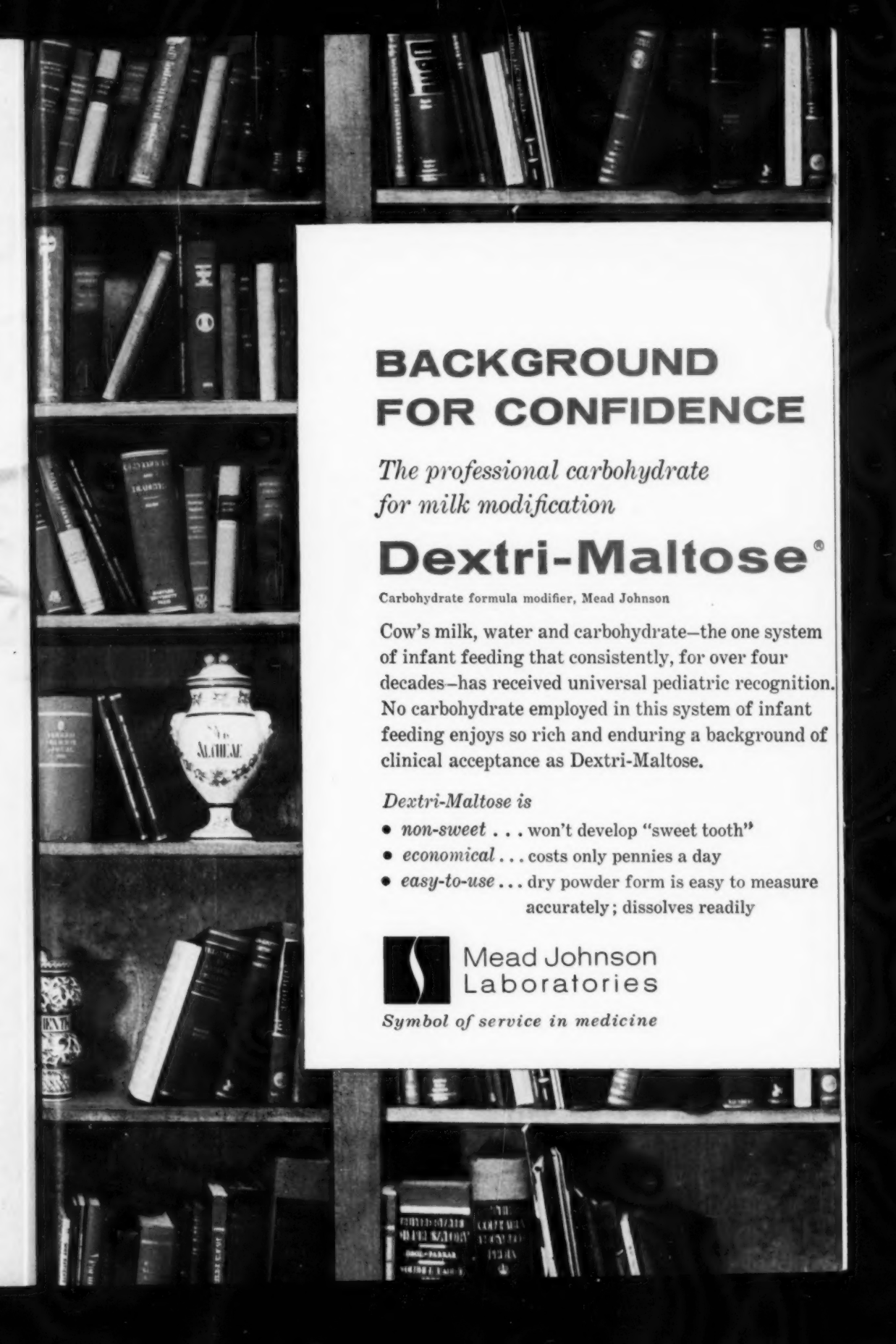
AND WHEN THE DIARRHEA IS BACTERIAL IN ORIGIN

Entoquel with Neomycin syrup

(Complete information regarding the use of Entoquel Syrup and Entoquel with Neomycin Syrup is available on request.)

Supplied: Entoquel Syrup – each 5 cc. contains 5 mg. thihexinol methylbromide, bottles of 6 oz. Entoquel with Neomycin Syrup – each 5 cc. contains 5 mg. thihexinol methylbromide and 50 mg. neomycin (from the sulfate), bottles of 6 oz. Available on Rx only.

WHITE LABORATORIES, INC., Kenilworth, New Jersey



BACKGROUND FOR CONFIDENCE

The professional carbohydrate for milk modification

Dextri-Maltose®

Carbohydrate formula modifier, Mead Johnson

Cow's milk, water and carbohydrate—the one system of infant feeding that consistently, for over four decades—has received universal pediatric recognition. No carbohydrate employed in this system of infant feeding enjoys so rich and enduring a background of clinical acceptance as Dextri-Maltose.

Dextri-Maltose is

- *non-sweet* . . . won't develop "sweet tooth"
- *economical* . . . costs only pennies a day
- *easy-to-use* . . . dry powder form is easy to measure accurately; dissolves readily

Mead Johnson Laboratories

Symbol of service in medicine

happy

rarely a "colicky" cry with Lactum

When Lactum was fed to 180 sick and 10 well infants, only 7 experienced "colic." Even the breast-fed infants admitted to the service and put on this formula did not reveal untoward symptoms.[1]

excellent digestibility

New methods of manufacture and modification of the milk reduce the curd tension of Lactum nearly to zero, thus enhancing digestibility.

higher protein for sturdy, satisfied babies

"Personal experience with the hunger of infants fed even 3.5 Gm. [of protein] per kilogram makes us unwilling to recommend intakes of cow's milk which would give less protein. Although the determinants of food intake are complex, the possibility exists that unmet nutritional needs may make the intake of 3.5 Gm. and more of cow's milk protein per kilogram necessary . . ."[2]

Lactum supplies the higher protein level of modified milk formulas that has been used so successfully in the feeding of infants. In Lactum 16% of total calories is derived from protein.

1. Henrickson, W. E.: GP *8*:51 (Oct.) 1953. 2. Gordon, H. H., and Ganzon, A. F.: J. Pediat. *54*:503 (April) 1959.

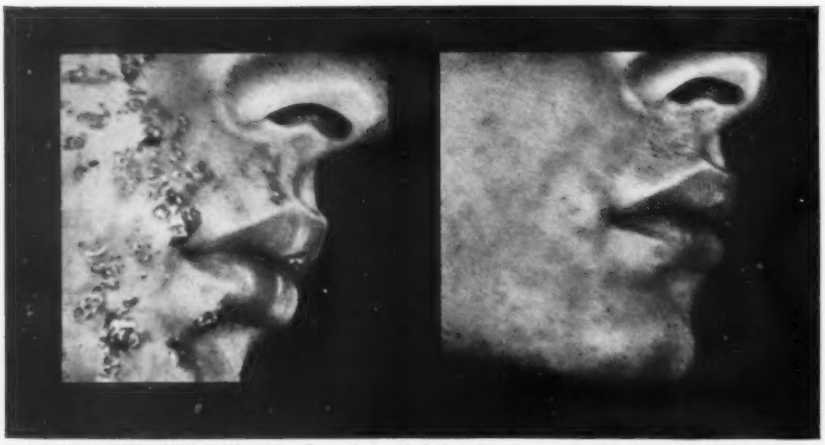
specify

Lactum®

Modified milk formula

Mead Johnson Laboratories

Symbol of service in medicine



Infectious folliculitis with secondary impetiginization treated with FURACIN-HC Cream *—6 days later improved and discharged.*

Pyodermas: fight infection, facilitate healing

In clinical use for more than 13 years and today the most widely prescribed single topical antibacterial, FURACIN *retains undiminished potency against pathogens such as staphylococci that no longer respond adequately to other antimicrobials.* FURACIN *is gentle, nontoxic to regenerating tissue, speeds healing through efficient prophylaxis or prompt control of infection. Unique water-soluble bases provide thorough penetration, lasting activity in wound exudates, without "sealing" the lesion or macerating surrounding tissue.*

Eaton®

the broad-spectrum bactericide exclusively for topical use

FURACIN®

brand of nitrofurazone

in dosage forms for every topical need

Soluble Dressing / Soluble Powder
Solution / Cream / HC Cream
(with hydrocortisone) / Vaginal
Suppositories / Inserts / FURESTROL®
Suppositories (with diethylstilbestrol)
Special Formulations for Eye, Ear, Nose

EATON LABORATORIES
Division of The Norwich Pharmacal Company
NORWICH, NEW YORK

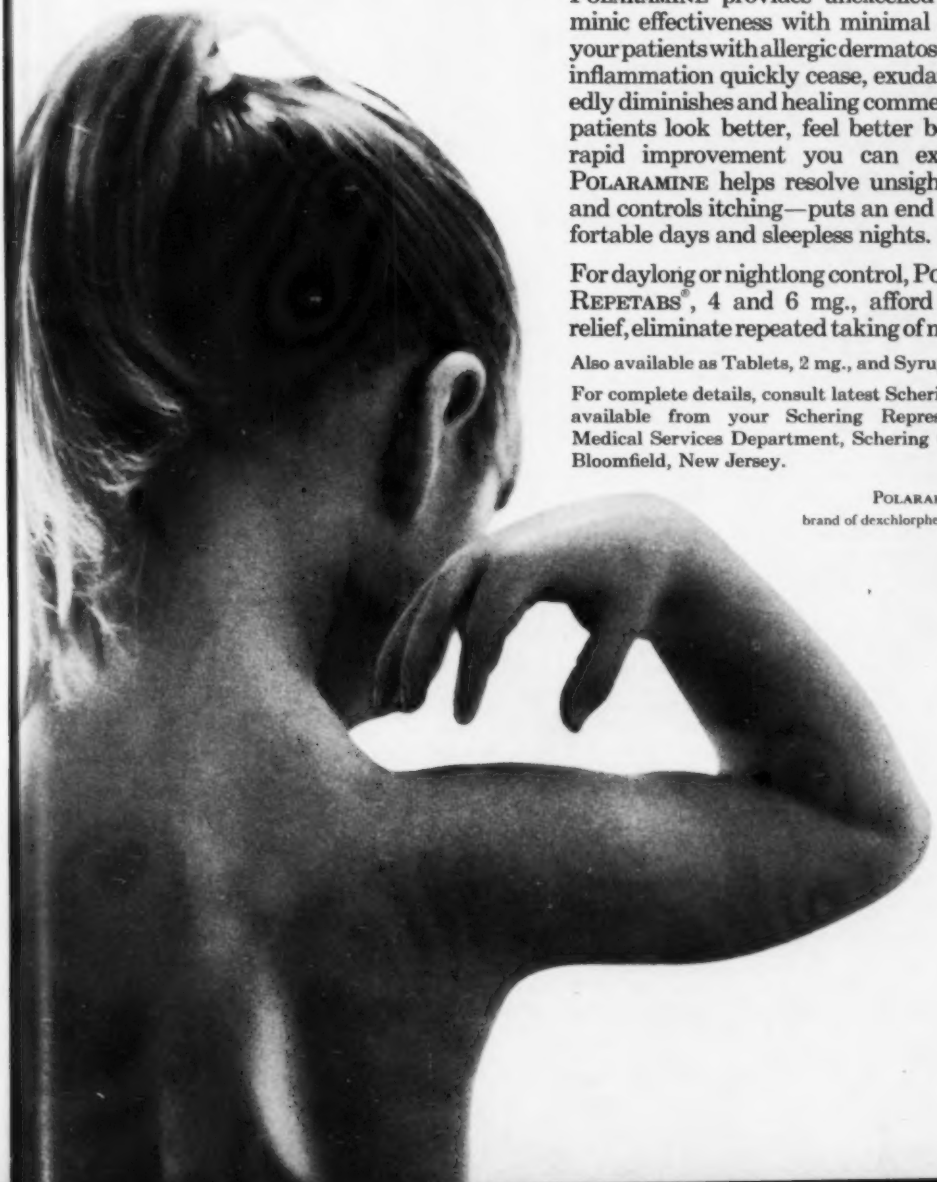
Schering

to scratch or not to scratch...?

in allergic dermatoses there is no question

POLARAMINE

rapid relief of itching, associated symptoms



POLARAMINE provides unexcelled antihistaminic effectiveness with minimal dosage for your patients with allergic dermatoses. Itching, inflammation quickly cease, exudation markedly diminishes and healing commences. Your patients look better, feel better because the rapid improvement you can expect with POLARAMINE helps resolve unsightly lesions and controls itching—puts an end to uncomfortable days and sleepless nights.

For daylong or nightlong control, POLARAMINE REPETABS®, 4 and 6 mg., afford prolonged relief, eliminate repeated taking of medication.

Also available as Tablets, 2 mg., and Syrup, 2 mg./5cc.

For complete details, consult latest Schering literature available from your Schering Representative or Medical Services Department, Schering Corporation, Bloomfield, New Jersey.

POLARAMINE® Maleate,
brand of dexchlorpheniramine maleate.

For Infants with Cow's Milk

ALLERGY

Miracle BRAND GOAT MILK

In most cases of *cow's milk allergy* hypersensitivity is due to the presence of lactoglobulin and lactalbumin. Both are species-specific proteins. *Goat Milk* contains lactoglobulin and lactalbumin with *different molecular composition* from that of cow's milk; therefore, it usually proves innocuous.

The transition from cow's milk to Goat Milk is natural and easy for the infant because Goat Milk, like human milk, forms a light, soluble, readily assimilated curd. Of course, MIRACLE Goat Milk is a natural milk food with all the intrinsic growth factors so essential in infancy. Specify MIRACLE Goat Milk—Evaporated or new Powdered form—Preferred for its uniform high quality.

Physicians' Samples

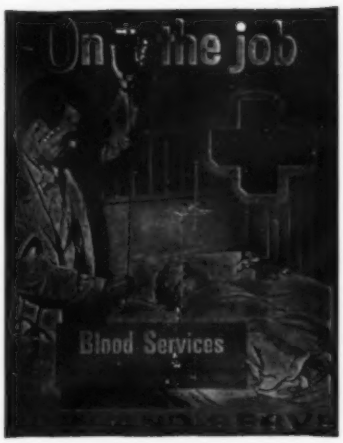
MILK FOODS, INC.
DEL MONTE RESEARCH PARK
MONTEREY, CALIF.

Please send me two sample cans of Miracle Evaporated Goat Milk.

Name_____

Address_____

City_____ State_____



Changing Your Address?

When you move, please—

(1) Notify us to change your address—allow us six weeks to make the change.

(2) Mention the name of this Journal. (We publish twelve periodicals.)

(3) Give us your old address. If possible, return the addressed portion of the envelope in which we sent your last copy.

(4) Give us your new address—complete—including the Postal zone number.

(5) Please print your name and address.

Thank You!

Circulation Department, The C. V. Mosby Company, Publishers, 3207 Washington Blvd., St. Louis 3, Mo.

INDEX TO ADVERTISERS

Actifed
Burroughs Wellcome & Co. (U.S.A.) Inc. ---------- 22

Actifed-C Expectorant
Burroughs Wellcome & Co. (U.S.A.) Inc. ---------- 85

Aerosporin
Burroughs Wellcome & Co. (U.S.A.) Inc. ---------- 74

Allergenic Extracts
Center Laboratories ---------- 90

Aquacort Jel
The William A. Webster Company ---------- Third Cover

Atarax
J. B. Roerig & Company ---- 28

Aveeno Bar
Aveeno Corporation ---------- 40

Aveeno Colloid Baths
Aveeno Corporation ---------- 39

Baby Foods
Heinz Baby Foods ---------- 53

Bacimycin
Walker Laboratories, Inc. ---- 47

Baker's Modified Milk
The Baker Laboratories, Inc. 68

BiB Juices
Edward Dalton Co. -------- 23

Bronkotab Elixir
Breon Laboratories Inc. ------ 8

Caldesene
Maltbie Laboratories ---------- 69

Carnation Evaporated Milk
Carnation Company ---------- 102

Celestone
Schering Corporation ------ 42, 43

Chel-Iron
Kinney & Company, Inc. ---- 81

Classified Advertisement
The Permanente Clinic ------ 100

Cor-D-Tar
Desitin Chemical Company --- 35

Cort-Dome
Dome Chemicals Inc. -------- 77

Cosa-Terrabon
Pfizer Laboratories --------- 48, 49

Cremomycin
Merck Sharp & Dohme ------ 80

Deca-Visol and Tri-Visol
Mead Johnson Laboratories ---------- 95, 96, 97

Declomycin
Lederle Laboratories ---------- 92

Desitin Powder
Desitin Chemical Company -- 58

Dextri-Maltose
Mead Johnson Laboratories -- 105

Diaper Pure
Central Drug ---------- 100

Diaparene
Breon Laboratories Inc. ------ 4

Diloderm
Schering Corporation -------- 55

Donnagel
A. H. Robins Company Inc. --- 46

Elixophyllin
Sherman Laboratories -------- 36

Emetrol
Kinney & Company, Inc. ---- 82

Enfamil
Mead Johnson Laboratories ---------- 60, 61, 62

E.N.T. Therapy
White Laboratories, Inc. ----- 57

Entoquel
White Laboratories, Inc. ----- 104

Feed-Rite Nipple
Davol Rubber Company ------ 10

Fleet-Enema
C. B. Fleet Co., Inc. -------- 50

Fostex
Westwood Pharmaceuticals ---- 51

Forhistal
Ciba Pharmaceutical Products - 66

Fulvicin
Schering Corporation ------- 101

Funda-Vite (F)
Hoyt Pharmaceutical Corp. -- 6

Furacin
Eaton Laboratories ---------- 108

Furadantin
Eaton Laboratories ---------- 11

Gantrisin
Roche Laboratories ---------- 103

Homicebrin
Eli Lilly and Company ------ 86

Infant-Formula Room
American Sterilizer ---------- 33

Kanana Banana Flakes
Kannengiesser & Co. -------- 41

Konakion
Roche Laboratories ---------- 27

Lactinex
Hynson, Westcott & Dunning, Inc. ---------- 70

Lactum
Mead Johnson Laboratories ---------- 106, 107

Livitamin
The S. E. Massengill Company ---------- 14, 15

Lowila Cake
Westwood Pharmaceuticals ---- 52

Mebaral
Winthrop Laboratories ------ 76

Medihaler
Riker Laboratories ---------- 93

Meprospan-400
Wallace Laboratories ---------- 13

Metiderm
Schering Corporation -------- 89

Miracle Goat Milk
Milk Foods, Inc. ---------- 110

Mulvidren
The Stuart Company -------- 12

Noctec
E. R. Squibb & Sons 2

Orange Juice
Florida Citrus Commission --- 26

Pablum
Edward Dalton Co. ---------- 94

Paladac
Parke, Davis & Company --- 37

Pediatric Urine Collectors
Sterilon Corporation ---------- 99

Pentids
E. R. Squibb & Sons ---- 54, 100

Polaramine
Schering Corporation ---------- 109

Pork
American Meat Institute ----- 34

Povan
Parke, Davis & Company ---- 63

Purivax
Merck Sharp & Dohme -- 64, 65

Quadrinal
Knoll Pharmaceutical Company 31

Quaker Oats
The Quaker Oats Company -- 83

Scotch Brand Surgical Tape Microporous
Minnesota Mining and Manufacturing Company -------- 67

Similac
Ross Laboratories ---------- 32

S-M-A
Wyeth Laboratories ------- 44, 45

Sobee
Mead Johnson Laboratories 24, 25

Soma
Wallace Laboratories ---------- 88

Staphcillin
Bristol Laboratories ---------- 16-21

Tacaryl
Mead Johnson Laboratories 78, 79

Terfonyl
E. R. Squibb & Sons -------- 91

Tigan
Roche Laboratories Second Cover

Tylenol
McNeil Laboratories, Inc. --- 87

Tyzine
Pfizer Laboratories -- Fourth Cover

Varamel
The Baker Laboratories, Inc. 75

Viacets
Walker Laboratories, Inc. ---- 84

Vifort
Endo Laboratories ---------- 56

Viokase
Viobin ---------- 90

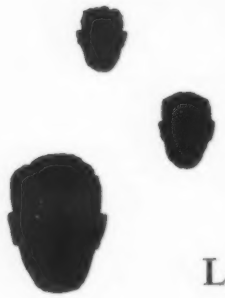
Vi-Penta/Zestabs
Roche Laboratories ---------- 59

Vi-Sols
Mead Johnson Laboratories 71-73

Xylocaine Viscous
Astra Pharmaceutical Products, Inc. ---------- 38

Zentron
Eli Lilly and Company ---- 29, 30

While every precaution is taken to insure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.



headache?
fever?
pain?
fatigue?

Learn the Best Way to Relieve the Discomfort from these Symptoms and Many Others from this Authoritative Guidebook

With medical literature concentrating on curing disease, the problem of how to give relief for the patient's symptoms usually receives scant attention. On the other hand, the advertising pages of our medical journals are often filled with somewhat indiscriminate recommendations for the use of drugs for the relief of symptoms and prescriptions for making the patient feel better. Now you can get help for this common dilemma from this authoritative new book.

Ready this Month! New 2nd Edition **Modell**

RELIEF OF SYMPTOMS

The new 2nd edition of this 425-page book is an authoritative but nevertheless a very practical, down-to-earth guide to aid you in the daily problems of relieving your patient's distress. It's a quick reference that can assist you in providing relief quickly and effectively before a diagnosis is made. In emergency situations, this book can tell you exactly how to relieve pain or discomfort until more satisfactory treatment is available.

Written in an informal and interesting style by Walter Modell, M.D., the well known author, and editor of CLINICAL PHARMACOLOGY AND THERAPEUTICS, this book discusses the relief of 27 specific symptoms in individual chapters which include well over 95% of those symptoms which bring patients to the doctor's office.

By WALTER MODELL, M.D., F.A.C.P. Ready later this month. 2nd edition, 425 pages, 6¾" x 9½", illustrated. About $11.50.

Order on 30 Day Approval!

THE C. V. MOSBY COMPANY
3207 Washington Blvd., St. Louis 3, Mo.

I accept your offer to examine a copy of the new 2nd edition of Modell, RELIEF OF SYMPTOMS, priced at about $11.50, on 30 day approval without charge or obligation. A remittance with this order will save the mailing charge.

☐ **Payment enclosed (Same return privilege)** ☐ **Charge my account** ☐ **Open a new account for me**

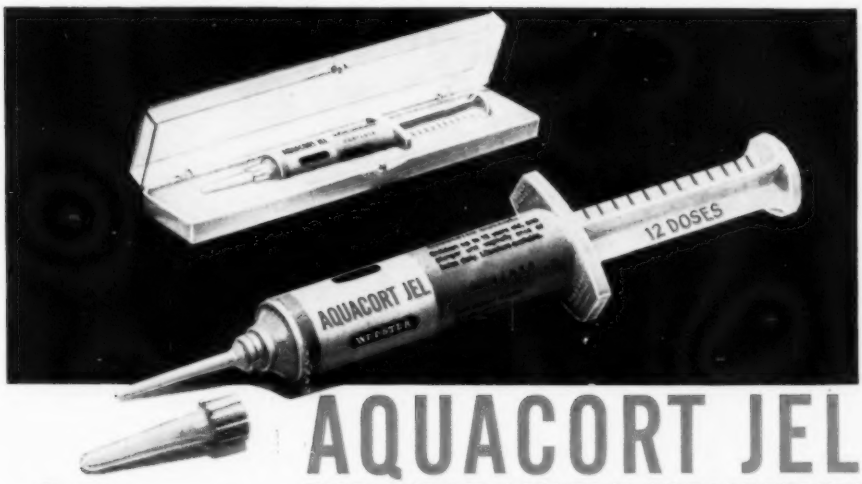
_____ **M.D.**

Address _____

City _____ **Zone** _____ **State** _____

This 30 day approval offer is limited to the continental U.S. only.

there IS
something new
under the sun!



AQUACORT JEL

THE FIRST SIMPLE APPLICATION FOR EFFECTIVE TREATMENT OF VAGINITIS IN YOUNG CHILDREN

The Aquacort Jel formula effectively combines hydrocortisone acetate, three bacteriacidal agents, urea and a spreading agent in a special, water-miscible base. This enhanced formulation is packaged in a syringe for ease of application to the immature vagina, thru a thin, flexible nozzle. The plunger in each syringe is graduated to expel the proper amount of medication for a thin covering of a small area.

For quick, positive relief in infants and young children: vulvovaginitis, non-specific vaginitis, allergic vaginitis, non-specific vulvitis, for eradication of trichomonads, monilia, mixed, and bacterial invaders.

DOSAGE: Infants under 1 yr. of age: one plunger unit (0.5 gm.) once or twice daily.

Children 1 to 12 yrs. of age: one or two plunger units (0.5 gm. to 1.0 gm.) once or twice daily.

Over 12 years of age and adult females: May use Aquacort Supprettes intravaginally once or twice daily instead of the jel.

SIDE EFFECTS: An occasional young patient experienced a transient, mild sting on the first application which quickly disappeared and no further burning occurred with repeated applications.

PRECAUTIONS: Aquacort Jel should not be used for a long, continuous period of time since sensitization to some of the incorporated drugs could result. Discontinue use if reaction occurs.

Active ingredients:

1. Tyrothricine U.S.P. 0.25 mg. (0.5%)
2. Phenylmercuric Acetate 0.5 mg. (0.10%)
3. 9-Amino acridine HCl 0.5 mg. (0.10%)
4. Polysorbate 80 U.S.P. 1.66 mg. (0.33%)
5. Urea 3.33 mg. (0.67%)

WEBSTER

4-1961 THE WILLIAM A. WEBSTER CO., MEMPHIS 3, TENNESSEE

BRAND OF TETRAHYDROZOLINE HYDROCHLORIDE (0.05%)

Tyzine®

pediatric nasal drops

promptly relieves nasal congestion caused by colds or allergy

virtually free of sting, burn and rebound congestion

IN BRIEF

TYZINE is tetrahydrozoline hydrochloride, a sympathomimetic amine with potent decongestant properties. Relief is almost immediate and lasts four to six hours after a single administration. Virtually free of sting or burn and rebound congestion . . . odorless and tasteless. TYZINE is not significantly absorbed systemically when used as directed . . . does not impair ciliary activity . . . and is physiologically buffered to pH 5.5.

INDICATIONS: Relieves inflammatory hyperemia and edema of the nasal mucosa and congestive obstruction of sinus and eustachian ostia, as may occur in the common cold, hay fever, perennial vasomotor rhinitis, chronic hypertrophic rhinitis, and sinusitis.

DOSAGE AND ADMINISTRATION: *Infants under 2 years*—1 or 2 drops. *Children 2 to 6 years*—2 or 3 drops. Instill in each nostril as needed, not more often than every three hours.

SIDE EFFECTS: Transient mild local irritation after instillation has been reported in rare instances.

PRECAUTIONS: Always use the 0.05% pediatric strength for infants and younger children. The 0.1% concentration of TYZINE should be restricted to adults and children 6 years and over. Avoid doses greater or more frequent than those recommended above. Use with caution in hypertensive and hyperthyroid patients. Overdosage may cause drowsiness, deep sleep, respiratory depression, marked hypotension or even shock in infants and young children. *KEEP OUT OF HANDS OF CHILDREN OF ALL AGES.*

SUPPLIED: TYZINE *Pediatric Nasal Drops*, ½-oz. bottles, 0.05%, with *calibrated* dropper. Also available: TYZINE *Nasal Solution*, 1-oz. dropper bottles, 0.1%. TYZINE *Nasal Spray*, 15 cc., in plastic bottles, 0.1%.

More detailed professional information available on request.

Science for the world's well-being™ Pfizer PFIZER LABORATORIES *Division, Chas. Pfizer & Co., Inc. Brooklyn 6, New York*

#652